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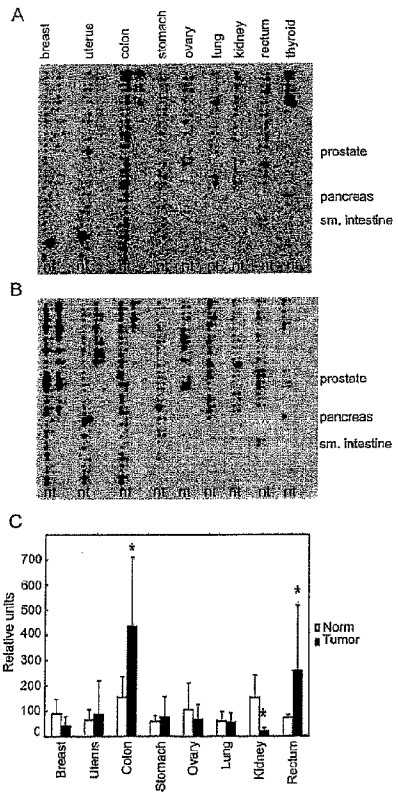

(57) Abstract: The invention provides materials and methods for colorectal cancer screening, diagnosis, and therapy.

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MATERIALS AND METHODS FOR COLORECTAL CANCER SCREENING, DIAGNOSIS, AND THERAPY

FIELD OF THE INVENTION

The present invention relates generally to methods and materials for altering colorectal cancer progression. The present invention also relates to techniques for screening for colon cancer and/or premalignancies.

BACKGROUND

The transcription factor Prox-1 is expressed in a number of tissues during embryonic development, including lens fiber cells, subpopulation of neurons in brains and neural tube, skeletal muscle, heart, liver, pancreas and lymphatic endothelial cells. Targeted inactivation of Prox-1 results in the defects of eye development because of the failure of lens fiber cells to elongate (Wigle et al., Nat. Genet. 21: 318-22, 1999). Prox-1 is also necessary for the migration of hepatocytes during liver development (Sosa-Pineda et al., Nat. Genet. 25: 254-5, 2000). In addition, Prox-1 deficient embryos lack lymphatic vasculature, while the blood vessel development is not affected (Wigle et al., Cell 98: 769-778, 1999).

Recently, others and we have demonstrated the essential role of Prox-1 in the regulation of the lymphatic endothelial phenotype. Overexpression of Prox-1 in blood vascular endothelial cells, where it is otherwise absent, leads to the increased expression of lymphatic endothelial markers and to the suppression of the genes characteristic for the blood vascular endothelial lineage (Petrova et al., Embo J. 21: 4593-9, 2002; Hong et al., Dev. Dyn. 225: 351-7, 2002).

Notch is a transmembrane protein that acts as a receptor in a cell-cell signaling mechanism, and in combination with other cellular factors, influences differentiation, proliferation and apoptotic events at all stages of development (Artavanis-Tsakonas, Science 284: 770-776, 1999). In animal models, mutations in the Notch receptor have resulted in developmental abnormalities (Joutel et al., Nature 383: 707, 1996; Li. et al., Nature Genet. 16:243, 1997).

Cancer treatments generally promote tumor regression by inhibiting tumor cell proliferation, inhibiting angiogenesis (growth of new blood vessels that is necessary to support tumor growth) and/or prohibiting metastasis by reducing tumor cell motility or invasiveness. Colon cancers are a very common malignancy and colon cancers are typically adenocarcinomas, or sometimes carcinoid tumors. Treatment is primarily surgical resection of the colon, although chemotherapy has been found to be beneficial in some cases. These treatment options for colon cancer are of unpredictable and sometimes limited value, especially if the cancer has not been identified and removed at early stages. There continues to exist a need for novel therapies and diagnostic methods for cancer conditions.

SUMMARY OF THE INVENTION

The present invention addresses one or more ongoing needs by providing materials and methods for screening for and treating cancerous and precancerous conditions, especially colorectal in nature.

As one aspect, the invention provides materials and methods to screen a mammalian subject for a cancerous or precancerous condition based on analysis of Prox-1 expression in cells from the mammalian subject. In particular, materials and methods are provided for screening colon tissue for signs of cancerous or precancerous pathology.

For example, the method includes a method of screening colon tissue for a pathological condition, said method comprising:

measuring Prox-1 expression in a biological sample that comprises colon tissue from a mammalian subject, wherein elevated Prox-1 expression in the colon tissue correlates with a pathological phenotype. The determination of elevated Prox-1 expression is generally made by way of a comparison, e.g., to a measurement of Prox-1 expression in healthy colon tissue (from the same subject or others of the same species, preferably matched for sex, age, race, or other characteristics); or to a measurement of Prox-1 expression in diseased (especially neoplastic) colon tissue. When comparing Prox-1 expression in the colon tissue to Prox-1 expression in healthy colon tissue, an increased (e.g., elevated) Prox-1 expression in the colon tissue

from the mammalian subject correlates with a pathological phenotype. When comparing to diseased tissue, comparable levels of expression in the tissue from the subject correlates with a pathological phenotype.

In another, related example, the invention includes a method of screening colon tissue for a pathological condition, the method comprising steps of: (a) obtaining a biological sample comprising colon tissue from a mammalian subject; (b) measuring Prox-1 expression in the colon tissue; and (c) screening for the presence or absence of a pathological condition from the measurement of Prox-1 in the sample.

Similarly, the invention includes a method of screening colon tissue for a pathological condition, the method comprising steps of: (a) obtaining a biological sample comprising colon tissue from a mammalian subject; (b) measuring Prox-1 expression in the colon tissue; and (c) comparing Prox-1 expression in the colon tissue to Prox-1 expression in healthy colon tissue, wherein increased Prox-1 expression in the colon tissue correlates with a pathological phenotype.

For this type of method, the term "pathological condition" is intended to include any abnormality or evidence of disease that warrants medical treatment or monitoring due to concern of developing disease. Cancers and precancerous changes in tissue are particularly contemplated. Thus, in preferred embodiments, the method can be characterized as a screen for colon cancer or colorectal cancers, and increased Prox-1 expression in the colon tissue is scored as being indicative of a cancerous or precancerous condition.

The method can be combined with any other molecular, cellular, pathological, or patient symptom criteria to assist a medical practitioner in early diagnosis and therapeutic or prophylactic therapy. For example, in one variation, the method further comprises measuring expression of at least one gene or protein selected from the group consisting of CD44, Enc1, and ID2 in the colon tissue, wherein elevated Prox-1 expression and elevated expression of the at least one gene/protein in the colon tissue correlate with a pathological phenotype. In another variation, the method further comprising measuring activation of -catenin/TCF pathway in the colon tissue, wherein activation of the -catenin/TCF pathway and

elevated Prox-1 expression in the colon tissue correlate with a pathological phenotype. Activation of the -catenin/TCF pathway can be measured by a variety of indicators, including mutations in an APC gene; mutations in a -catenin gene; and nuclear localization of -catenin.

The biological sample is any tissue or fluid sample obtained in any way from a mammalian subject that includes cells from the large intestine. Biopsies or other surgically removed specimens are preferred. Stool or feces may contain sufficient colon tissue for some embodiments of the assay.

The assay may be performed on any mammalian subject, including laboratory animals used in cancer research, livestock, and domestic pets. Humans are most preferred.

Any available technique can be used for measuring Prox-1 expression, including direct and indirect techniques. For example, in one variation, the measuring comprises measuring Prox-1 protein in the biological sample. Preferred techniques for measuring amounts or concentrations of Prox-1 protein in a sample are immunological techniques that involve use of a polyclonal or monoclonal antibody that specifically binds Prox-1, or use of a Prox-1-binding fragment of such an antibody. For example, the measuring comprises contacting the colon tissue with a Prox-1 antibody or antigen-binding fragment thereof. Quantification of the amount of bound antibody (e.g., using a label or second, labeled antibody) provides a measurement of Prox-1 protein expressed in the sample. Immunoassays such as radioimmunoassay, immunoradiometric assay (labeled antibody), or an enzyme-linked immunosorbent assay (ELISA) are contemplated.

In another variation, the measuring comprises measuring Prox-1 mRNA in the colon tissue. Elevated levels of Prox-1 mRNA in the sample are scored as elevated Prox-1 expression. Any available assay for measuring specific oligonucleotides is suitable. Preferred materials for such measurements are oligonucleotide probes complementary to all or a portion of the Prox-1 mRNA sequence. Probes of at least 14 and more preferably 18 nucleotides are preferred to assure specificity. One technique for measuring Prox-1 mRNA comprises *in situ* hybridization to measure Prox-1 mRNA in the colon sample. Other techniques

involve steps of isolating mRNA from the colon tissue and measuring Prox-1 mRNA in the isolated mRNA, for example, by Northern hybridization procedures. In still another variation, quantitative reverse transcriptase polymerase chain reaction (PCR), real-time PCR, or other PCR techniques are employed to quantitatively amplify Prox-1 mRNA (relative to control samples) to provide a quantitative measurement of Prox-1 mRNA in the colon tissue.

In yet another embodiment, Prox-1 expression is measured indirectly by measuring a functional property of Prox-1, such as measuring Prox-1 binding to DNA or downstream Prox-1 transcription factor effects.

The screening method further includes a comparing step whereby Prox-1 expression in the colon tissue is compared to Prox-1 expression in healthy colon tissue, wherein increased Prox-1 expression in the colon tissue correlates with a pathological phenotype. As described herein, Prox-1 expression is elevated in a statistically significant manner in pathological specimens studied, compared to healthy colon tissue samples. In one variation, the comparison is performed by taking simultaneous or sequential measurements of a test sample and a sample of colon tissue that is known to be taken from healthy tissue. In another variation, data is accumulated on the quantity of Prox-1 mRNA or protein in healthy tissues, and the amount that is measured in the colon tissue from the biological sample is compared to this predetermined amount. It will be appreciated that comparing Prox-1 measurements from a test sample to measurements from a cancerous or precancerous condition can provide an equivalent indication of the presence or absence of the pathological condition, wherein a test sample with Prox-1 expression comparable to the elevated level observed in a cancer correlates with a pathological phenotype.

For measurement comparisons, a database of Prox-1 measurements from colon tissues can be developed, preferably containing information about healthiness or disease of the tissue; age, sex, race/ethnicity of the donor, and location from which the sample was taken. With a database of samples, comparisons can be analyzed using statistical analysis to determine the statistical significance of a measurement's deviation from a mean, optionally selecting entries from the database by selecting for the patient's age, sex, ethnicity, and other factors to best match the patient (mammalian subject) being tested. Such statistical analysis permits

establishment of one or more "cutoff" values for the Prox-1 measurement that are correlated with a likelihood of having, or developing, a cancerous condition.

If elevated Prox-1 is detected, then in a preferred embodiment, the method further comprises a step of administering to a human subject identified as having a pathological condition characterized by increased Prox-1 expression in colon tissue a composition comprising a Prox-1 inhibitor.

In a related embodiment, the invention provides a method of inhibiting the growth of colon cancer cells, such as colon carcinoma cells, colon adenoma cells, or colon adenocarcinoma cells in a mammalian subject comprising a step of:

administering to the subject a composition comprising a molecule that suppresses expression of Prox-1, thereby inhibiting the growth of colon carcinoma cells.

For reasons of cost, safety, and efficacy, it is becoming increasingly preferred to attempt to identify patients most likely to benefit from a therapeutic regimen before administering it. This is especially true with cancers where it is known that not all patients respond the same to all therapies. Thus, in a preferred variation of the method, steps are taken to identify patients most likely to benefit from this regimen. For example, the method further comprises a step of identifying a mammalian subject with a colon cancer characterized by increased Prox-1 expression. The composition is administered to such a patient after the identifying step, because cancers characterized by the elevated expression are expected to be the cancers most likely to respond to the inhibitors. Exemplary cancers (neoplasms) in which Prox-1 elevation has been observed include colorectal adenomas and colorectal carcinomas, as described below in greater detail.

The composition to be administered preferably includes, in addition to the Prox-1 inhibitor, a pharmaceutically acceptable diluent, adjuvant, or carrier medium. The composition optionally includes additional antineoplastic agents.

Administration of any Prox-1 inhibitors, alone or in combination, is contemplated for this invention, either alone or in combination with other Prox-1 inhibitors or other antineoplastic agents. Exemplary inhibitor molecules include antisense oligonucleotides that inhibit Prox-1 expression; micro-RNA that inhibits

Prox-1 expression; small (short) interfering RNA (siRNA) that inhibit Prox-1 expression (e.g., siRNA that comprise at least one nucleotide sequence set forth in SEQ ID NOS: 4, 5, 6, and 7); zinc finger proteins that inhibit Prox-1 expression; polypeptides that act as dominant negative form of Prox-1 protein, such as Prox-1 forms that have a disrupted DNA binding domain or transactivation domain(s); polynucleotides that encode dominant-negative Prox-1 proteins; Prox-1 antibodies and fragments thereof; polynucleotides that encode Prox-1 antibodies or encode polypeptides that comprise Prox-1 binding domains; small molecules discovered and designed through screening based on the teachings herein, and so on. U.S. Patent Application Publication No. 2003/0224516 discloses exemplary molecules for inhibiting Prox-1 expression and is incorporated herein by reference.

The inhibitor is preferably administered in an amount and in a regimen that halts or inhibits neoplastic growth of the affected colorectal tissue. As another benchmark, the tissue itself preferably reverts to a non-transformed, more healthy looking phenotype. As described herein, one apparent benchmark of beneficial administration is an increase in Notch-1 signaling. Thus, in one variation, the composition is administered in an amount effective to suppress Prox-1 expression and increase Notch 1 signaling.

Other indications of efficacy relate to modulation of prostaglandin synthesis. Thus, in another variation, the composition is administered in an amount effective to increase 15-PDGH activity or decrease prostaglandin D2 synthase activity.

As described herein and in literature, colorectal cancers also are often characterized by increases in the -catenin/TCF signaling pathway, relative to what is observable in healthy colorectal tissue. Thus, in a preferred variation, in addition to administering a Prox-1 inhibitor composition, the regimen further comprises administering to the subject an inhibitor of the -catenin/TCF signaling pathway. (Optionally, the patient's diseased tissue is first pre-screened for elevated expression/signaling of this pathway.) The categories of inhibitors described above for Prox-1 are specifically contemplated for the -catenin/TCF pathway as well. In one variation, the inhibitor of the -catenin/TCF signaling pathway is dominant

negative form of TCF-4. The inhibitor optionally targets (inhibits) TCF-4, ß-catenin, or c-myc expression or activity.

In yet another variation, administration of the Prox-1 inhibitor is combined with administration of a COX-2 inhibitor, such as any of the increasing class of non-steroidal anti-inflammatory agents.

In still another variation, administration of the Prox-1 inhibitor is combined with administration of a Notch signaling pathway agonist, such as a Notch ligand or expression vector to cause expression of a Notch ligand. Exemplary Notch ligands include Jagged1, Jagged2, Delta1, Delta3, Delta4, or Serrate.

Also contemplated is administration of a molecule that comprises an inhibitor of DNA methyltransferases. Such inhibitors are themselves contemplated as efficacious for inhibiting Prox-1 expression, and can be combined with any other Prox-1 inhibitor described herein for combination therapy. An exemplary methyltransferase inhibitor is 5-aza-2'-deoxycytidine.

In still another variation, the Prox-1 inhibitor composition is administered in combination with any known antineoplastic agent that is used in cancer therapy.

In still another variation, the Prox-1 inhibitor and/or Cox-2 inhibitor are combined (in a medicament or as a combination therapy) with an agent that induces differentiation in colorectal cancer cell lines. Exemplary agents include 1,25-dihydroxyvitamin D3 and analogs thereof; butyrate; and retinoids.

With respect to any combination treatment or therapy regimens described herein, the Prox-1 inhibitor composition can be administered simultaneously with the other active agents, which may be in admixture with the Prox-1 inhibitor, or may be in a separate composition. Each composition preferably includes a pharmaceutically acceptable diluent, adjuvant, or carrier. When the agents are separately administered, they may be administered in any order.

In still another embodiment, the invention includes a method of inhibiting Prox-1 function in a mammalian subject having a disease characterized by of Prox-1 over-expression in cells, comprising the step of administering to said

mammalian subject a composition, said composition comprising a compound effective to inhibit Prox-1 function in cells.

In still another variation, the invention includes the use of a Prox-1 inhibitor in the manufacture of a medicament for the treatment of a disease characterized by Prox-1 over-expression in cells, especially cancerous or precancerous cells of colorectal origin. The medicament optionally includes the additional agents described above, either in admixture with the Prox-1 inhibitor or separated, yet packaged together (preferably with instructions for treating the disease).

In yet another embodiment, the invention provides a method of screening for Prox-1 modulators comprising the steps of: (a) contacting a test molecule with Prox-1 protein, or a nucleic acid comprising a nucleotide sequence that encodes Prox-1 protein, under conditions which permit the interaction of the test molecule with the Prox-1 protein or nucleic acid; and (b) measuring the interaction between the test molecule and Prox-1 protein or the nucleic acid, wherein a test molecule that binds the Prox-1 protein or nucleic acid is identified as a Prox-1 modulator.

"Test molecule" refers to the molecule that is under evaluation for the ability to modulate (i.e., increase or decrease) the activity of Prox-1 protein. Most commonly, a test molecule that is a Prox-1 modulator will interact directly with Prox-1. However, the screens described herein can identify test molecules that modulate Prox-1 protein activity indirectly, such as by affecting Prox-1 gene expression. The screens work with essentially any test molecule, and the invention is not limited in this manner. In preferred embodiments, the test molecule is a protein, a carbohydrate, a lipid, or a nucleic acid. Molecules which regulate Prox-1 expression include nucleic acids which are complementary to nucleic acids encoding a Prox-1 protein, or are complementary to nucleic acid sequences which direct or control the expression of Prox-1 protein, and which act as anti-sense regulators of expression. The test molecule may be a member of a chemical library, such as libraries commonly maintained in large pharmaceutical companies or libraries generated combinatorially. In alternate embodiments, the test molecule interacts with Prox-1 by binding to the Prox-1 DNA binding domain, thereby effecting Prox-1 activity.

With respect to the screening methods described herein, it may be desirable to evaluate two or more test compounds together for their ability to increase or decrease the Prox-1 protein activity or expression. The assays set forth herein can be readily modified by adding such additional test compounds either simultaneous with, or subsequent to, or prior to, the first test compound. In additional embodiments, the measurement of the interaction of test molecules with Prox-1 may is carried out using solution-phase assays or immunoassays. In other embodiments, measurement of the interaction of test molecules with Prox-1 is carried out by evaluating biological activity of Prox-1.

In a related embodiment, the invention provides a method of screening for modulators of binding between a DNA and Prox-1 protein comprising steps of: (a) contacting a DNA with a Prox-1 protein in the presence and in the absence of a putative modulator compound; (b) detecting binding between the DNA and the Prox-1 protein in the presence and absence of the putative modulator compound; and (c) identifying a modulator compound based on a decrease or increase in binding between the DNA and the Prox-1 protein in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

In a related variation, molecules that modulate binding between DNA and Prox-1 are formulated into a composition or a growth media for contacting a cell from a colorectal cancer or colorectal cancer cell line, and a modulator that inhibits growth of the cell is selected as a preferred modulator for development as a therapeutic.

In yet another related embodiment, the invention provides a method of screening for modulators of binding between a DNA and Prox-1 protein comprising steps of: (a) contacting a DNA with a Prox-1 protein in the presence and in the absence of a putative modulator compound; (b) detecting binding between the DNA and the Prox-1 protein in the presence and absence of the putative modulator compound; and (c) identifying a modulator compound based on a decrease or increase in differentiation in the presence of the putative modulator compound, as compared to differentiation in the absence of the putative modulator compound.

In vivo screening also is contemplated, either in addition to or in place of *in vitro* screening. The test compound preferably is formulated into a pharmaceutically

acceptable diluent, adjuvant, or carrier. In a preferred variation, this formulation is administered to a mammal with pathological (e.g., cancerous) Prox-1 expressing colon tissue, and the efficacy of the formulation at inhibiting disease progression is monitored. For example, a method described above optionally further comprises steps of formulating a composition comprising the selected Prox-1 modulator and a pharmaceutically acceptable carrier; administering the composition to a mammalian subject having a colorectal cancer; and monitoring the mammalian subject for growth, metastasis, shrinkage, or disappearance of the colorectal cancer.

"Putative modulator compounds" are analogous to the "test molecules" described above in that they are alleged to have an effect on Prox-1 protein activity and are being identified as such using the methods described herein. In certain embodiments detecting DNA binding to Prox-1 protein and identifying an increase or decrease of DNA binding to Prox-1 protein employs immuno-based assays or various other assays that measure biological activity. Likewise, embodied by the invention are methods wherein identifying a modulator compound the use of proliferation and/or differentiation assays.

In still another variation of the invention, provided are short interfering RNA (siRNA) molecules that down regulate expression of Prox-1 by RNA interference. The siRNA molecule can be adapted for use to treat colorectal cancer and any other indications that respond to the level of Prox-1. The siRNA molecule comprises a sense region and an antisense region. The antisense region comprises sequence complementary to an RNA sequence encoding Prox-1, or a fragment thereof, and the sense region comprise sequence complementary to the antisense region. In additional embodiments, the siRNA molecule can comprise two nucleic acid fragments, wherein one fragment comprises the sense region and the second fragment comprises the antisense region of said siRNA molecule.

In one embodiment, a siRNA molecule of the invention can comprise any contiguous Prox-1 sequence. Preferably, the siRNA constructs are between 18 and 100 nucleotides in length. More preferably, the siRNA constructs are 21 nucleotides in length. In still another embodiment, the sense region of a siRNA molecule of the invention comprises a 3'-terminal overhang and the antisense region comprises a 3'-terminal overhang. The 3'-terminal overhangs each are preferably from 1 to 5

nucleotides. More preferably, the 3'-terminal overhangs are 2 nucleotides. In a preferred embodiment, the antisense region of the 3'-terminal nucleotide overhang is complementary to RNA encoding Prox-1.

With respect to the antisense region of the siRNA constructs, the antisense region of Prox-1 siRNA constructs can comprise a sequence complementary to sequence having any of SEQ ID NOs. 4 and 6. Further, the antisense region of Prox-1 siRNA constructs can comprise a having any of SEQ ID NOs. 5 and 7.

In yet an additional embodiment of the invention, compounds, particularly antisense oligonucleotides, which are targeted to a nucleic acid encoding Prox-1, and which modulate the expression of Prox-1 are provided. The antisense oligonucleotides of the invention are preferably complementary to (at least a segment of) the genomic Prox-1 sequence set forth as SEQ ID NO:1. mRNA splice sites, i.e., intron-exon junctions, may be preferred target regions. Accordingly, in another embodiment, the antisense oligonucleotides of the invention comprise a region complementary to a promoter or other control region, an exon, an intron, or an exon-intron boundary. Also embodied by the present invention are antisense oligonucleotides that are complementary to a region within 20-200 bases of an exon-intron splice junction. As detailed herein, pharmaceutical compositions comprising antisense oligonucleotides are also provided.

The foregoing paragraphs are not intended to define every aspect of the invention, and additional aspects are described in other sections, such as the Detailed Description. The entire document is intended to be related as a unified disclosure, and it should be understood that all combinations of features described herein are contemplated, even if the combination of features are not found together in the same sentence, or paragraph, or section of this document. Where protein therapy is described, embodiments involving polynucleotide therapy (using polynucleotides that encode the protein) are specifically contemplated, and the reverse also is true.

In addition to the foregoing, the invention includes, as an additional aspect, all embodiments of the invention narrower in scope in any way than the variations defined by specific paragraphs above. For example, certain aspects of the invention that are described as a genus, and it should be understood that every

member of a genus is, individually, an aspect of the invention. Although the applicant(s) invented the full scope of the invention described herein, the applicants do not intend to claim subject matter described in the prior art work of others. Therefore, in the event that statutory prior art within the scope of a claim is brought to the attention of the applicants by a Patent Office or other entity or individual, the applicant(s) reserve the right to exercise amendment rights under applicable patent laws to redefine the subject matter of such a claim to specifically exclude such statutory prior art or obvious variations of statutory prior art from the scope of such a claim. Variations of the invention defined by such amended claims also are intended as aspects of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A, 1B, and 1C depict the elevated Prox-1 mRNA levels in colorectal tumors. A cancer RNA profiling array was hybridized to probes for Prox-1 (Fig. 1A) and the lymphatic endothelial marker LYVE-1 (Fig. 1B). Fig. 1C illustrates the quantification of dot blot in Fig. 1A, the asterisk indicating tumor samples in which Prox-1 expression is significantly different from that of the normal tissue ($P<0.005$).

Figures 2A-2I depict Prox-1 expression patterns in colon cancer and normal colonic epithelium. Frozen sections of colon adenomas (Fig. 2A-C) or adenocarcinomas (Fig. 2D-F) and the corresponding normal tissues (Fig. 2H-I) were stained for Prox-1. Fig. 2C and Fig. 2I show high power magnification of adenoma and normal colon sections.

Figure 3 depicts the efficacy of Prox-1 suppression for inhibiting SW480R cell growth in soft agar. SW480R cells were transfected with GFP siPRNA, Prox-1siRNA A16 or Prox-1 siRNA A25 or left untreated, and seeded in soft agar in triplicate. The number of colonies was scored after two weeks of growth.

DETAILED DESCRIPTION

Demonstrated herein for the first time is the importance of Prox-1 in cancer. The Prox-1 gene and protein is overexpressed in colorectal cancers, as compared to healthy colon tissue and other cancer tissues. Prox-1 was overexpressed in 68% of colorectal carcinomas and in 80% of premalignant lesions that were examined, indicating that Prox-1 is important for tumorigenesis, and therefore a useful marker for screening and a useful target for intervention. In normal colonic epithelium, Prox-1 expression was restricted to two cell types, neuroendocrine cells and non-proliferating cells at the very base of the colonic crypts, a location that corresponds to the stem cell compartment. Contemplated and provided for in the present invention are polynucleotides and polypeptides for screening and diagnosis of colorectal cancer and/or premalignancies.

Intervention to suppress Prox-1 expression in colorectal cells resulted in increased activation of Notch signal transduction. Specifically, ablation of Prox-1 resulted in cell growth arrest and increased expression of epithelial markers. This was accompanied by an upregulation of the cell cycle inhibitor p21cip1, which has been shown to be important for the differentiation of intestinal epithelia (Quaroni et al., *Am. J. Physiol. Cell Physiol.* 279: C1045-57, 2000; Yang et al., *Cancer Res.* 61, 565-9, 2001), and by an increased expression of components of the Notch signaling pathway. Unexpectedly, this phenotype persisted for up to two weeks after transient transfection with Prox-1 siRNAs, demonstrating profound changes in the transcriptional program induced in the absence of Prox-1. Without intending to be limited to a particular theory or mechanism, Prox-1 may be involved in the maintenance of an undifferentiated state of colonic intestinal stem cells, and overexpression of Prox-1 in cancer cells and resulting inhibition of the Notch signaling pathway may lead to the de-differentiation frequently observed upon malignant transformation. The suppression of Prox-1 expression also negatively regulates prostaglandin activity in the tumor cell lines studied. It is, therefore, contemplated that suppression of Prox-1 or activation of Notch signaling in tumor cells can provide a differentiation therapy for colon carcinoma. The present invention, more specifically, provides compositions and methods for suppressing Prox-1 expression.

A. Inhibitory Nucleic Acid Constructs for the Suppression of Prox-1 Expression

As discussed herein, Prox-1 is overexpressed in colorectal cancer cells and suppression of Prox-1 expression results in increased Notch signal transduction and modified expression of enzymes of the prostaglandin biosynthetic pathway. This data provides an indication to disrupt the expression or activity of Prox-1 as a method of alleviating the symptoms of and/or inhibiting the growth or metastasis of colon cancer. Such disruption is achieved using any materials or methods available to inhibit Prox-1 mRNA or protein expression, or inhibit Prox-1 binding, and any Prox-1 activity. The present section discusses nucleic acid-based methods of disrupting the expression of Prox-1. Polynucleotide products which are useful in this endeavor include antisense polynucleotides, ribozymes, small interfering RNAs, natural or designed microRNAs, triple helix polynucleotides, and novel transcription factors that modulate the expression of Prox-1 protein.

Techniques for making and delivering antisense polynucleotides and ribozymes are well known to those in the art and have been extensively described in scientific, patent, and trade literature. (PCT Publication No. WO 00/32765; (*J Biol Chem* ;272:626-38. 1997); Kurreck *et al.*, (*Nucleic Acids Res.* ;30:1911-8. 2002); Crooke and B. Lebleu, eds. Antisense Research and Applications (1993) CRC Press; and Antisense RNA and DNA (1988) D. A. Melton, Ed. Cold Spring Harbor Laboratory Cold Spring Harbor, N.Y.) Anti-sense RNA and DNA molecules act to directly block the translation of mRNA by binding to targeted mRNA and preventing protein translation. An example of an antisense polynucleotide is an oligodeoxyribonucleotide derived from the translation initiation site, *e.g.*, between -10 and +10 regions of the relevant nucleotide sequence. Antisense oligonucleotides of 8-200 nucleotides in length that include at least a portion of this region of the Prox-1 cDNA or genomic sequences set forth as SEQ ID NOs: 1 and 2 (or are complementary to) are preferred Prox-1 inhibitors of the invention.

Antisense polynucleotides are typically generated within the cell by expression from antisense constructs that contain the antisense nucleic acid strand as the transcribed strand. Antisense methodology takes advantage of the fact that nucleic acids tend to pair with "complementary" sequences. By complementary, it is

meant that polynucleotides are those which are capable of base-pairing according to the standard Watson-Crick complementarity rules. That is, the larger purines will base pair with the smaller pyrimidines to form combinations of guanine paired with cytosine (G:C) and adenine paired with either thymine (A:T) in the case of DNA, or adenine paired with uracil (A:U) in the case of RNA. Inclusion of less common bases such as inosine, 5-methylcytosine, 6-methyladenine, hypoxanthine and others in hybridizing sequences does not interfere with pairing.

Targeting double-stranded (ds) DNA with polynucleotides leads to triple-helix formation; targeting RNA will lead to double-helix formation. Antisense polynucleotides, when introduced into a target cell, specifically bind to their target polynucleotide and interfere with transcription, RNA processing, transport, translation and/or stability. Antisense RNA constructs, or DNA encoding such antisense RNA's, may be employed to inhibit gene transcription or translation or both within a host cell, either *in vitro* or *in vivo*, such as within a host animal, including a human subject.

Antisense constructs may be designed to bind to the promoter and other control regions, exons, introns or even exon-intron boundaries of a gene. Highly effective antisense constructs include regions complementary to intron/exon splice junctions. Thus, a preferred embodiment includes an antisense construct with complementarity to regions within 50-200 bases of an intron-exon splice junction. It has been observed that some exon sequences can be included in the construct without seriously affecting the target selectivity thereof. The amount of exonic material included will vary depending on the particular exon and intron sequences used. One can readily test whether too much exon DNA is included simply by testing the constructs *in vitro* to determine whether normal cellular function is affected or whether the expression of related genes having complementary sequences is affected.

For purposes of making antisense oligonucleotides, polynucleotide sequences that are substantially complementary over their entire length and have zero or very few base mismatches are preferred. For example, sequences of fifteen bases in length preferably have complementary nucleotides at thirteen or fourteen or fifteen positions. Naturally, sequences which are completely complementary will be sequences which are entirely complementary throughout their entire length and have no base mismatches. Other sequences with lower degrees of homology also are

contemplated. For example, an antisense construct which has limited regions of high homology, but also contains a non-homologous region (*e.g.*, ribozymes) could be designed. These molecules, though having less than 50% homology, would bind to target sequences under appropriate conditions.

Methods for designing and optimizing antisense nucleotides are described in Lima et al., (J Biol Chem; 272:626-38. 1997) and Kurreck et al., (Nucleic Acids Res.; 30:1911-8. 2002). Additionally, commercial software and online resources are available to optimize antisense sequence selection and also to compare selected sequences to known genomic sequences to help ensure uniqueness/specificity for a chosen gene. (See, e.g., world wide web at sfold.wadsworth.org/index.pl.) Such uniqueness can be further confirmed by hybridization analyses. Antisense nucleic acids are introduced into cells (e.g., by a viral vector or colloidal dispersion system such as a liposome).

The genomic contig of chromosome 1 (where Prox-1 is located), cDNA for Prox-1, and protein sequences for Prox-1 (SEQ ID NOs: 1, 2, and 3, respectively) are published and disclosed as Genbank Accession Numbers NT_021877, NM_002763, and NM_002763, respectively. The Genbank Database is accessible on the world wide web at ncbi.nlm.nih.gov. Related Prox-1 protein and/or nucleic acid sequences from other sources may be identified using probes directed at these sequences. Such additional sequences may be useful in certain aspects of the present invention. Although antisense sequences may be full length genomic or cDNA copies, they also may be shorter fragments or oligonucleotides *e.g.*, polynucleotides of 100 or less bases. Although shorter oligomers (8-20) are easier to make and more easily permeable *in vivo*, other factors also are involved in determining the specificity of base pairing. For example, the binding affinity and sequence specificity of an oligonucleotide to its complementary target increases with increasing length. It is contemplated that oligonucleotides of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, or more base pairs will be used.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. The cleavage event renders the mRNA unstable and prevents protein expression. The mechanism of ribozyme action involves sequence specific interaction of the ribozyme molecule to complementary target RNA, followed

by an endonucleolytic cleavage. Within the scope of the invention are engineered hammerhead, for which the substrate sequence requirements are minimal, or other motif ribozyme molecules that specifically and efficiently catalyze endonucleolytic cleavage of RNA sequences encoding protein complex components. Design of the hammerhead ribozyme and the therapeutic uses of ribozymes are disclosed in Usman et al., Current Opin. Struct. Biol. (1996) 6:527-533. Ribozymes can also be prepared and used as described in Long et al., FASEB J. (1993) 7:25; Symons, Ann. Rev. Biochem. (1992) 61:641; Perrotta et al., Biochem. (1992) 31:16-17; Ojwang et al., Proc. Natl. Acad. Sci. (USA) (1992) 89:10802-10806; and U.S. Pat. No. 5,254,678. Methods of cleaving RNA using ribozymes is described in U.S. Pat. No. 5,116,742; and methods for increasing the specificity of ribozymes are described in U.S. Pat. No. 5,225,337 and Koizumi et al., Nucleic Acid Res. (1989) 17:7059-7071. Preparation and use of ribozyme fragments in a hairpin structure are described by Chowrira and Burke, Nucleic Acids Res. (1992) 20:2835. Ribozymes can also be made by rolling transcription (Daubendiek and Kool, Nat. Biotechnol. (1997) 15(3):273-277).

The full-length gene need not be known in order to design and use specific inhibitory ribozymes. Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites which include the following sequences, GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides corresponding to the region of the target gene containing the cleavage site may be evaluated for predicted structural features, such as secondary structure, that may render the oligonucleotide sequence unsuitable. The suitability of candidate targets may also be evaluated by testing their accessibility to hybridization with complementary oligonucleotides, using ribonuclease protection assays (Draper PCT WO 93/23569; and U.S. Pat. No. 5,093,246, incorporated herein by reference). Using the nucleic acid sequences disclosed herein and methods known in the art, ribozymes can be designed to specifically bind and cut the corresponding mRNA species. Ribozymes, therefore, provide a means to inhibit the expression Prox-1.

Alternatively, endogenous gene expression can be reduced by inactivating or "knocking out" the gene or its promoter using targeted homologous recombination. (E.g., see Smithies et al., 1985, Nature 317:230-234; Thomas &

Capecchi, 1987, Cell 51:503-512; Thompson et al., 1989 Cell 5:313-321). For example, a mutant, non-functional gene (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous gene (either the coding regions or regulatory regions of the gene) can be used to transfect cells that express that gene *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the gene.

Gene expression can also be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of the target gene (i.e., the gene promoter and/or enhancers) to form triple helical structures that prevent transcription of the gene in target cells in the body. (See generally, Helene, C. 1991, Anticancer Drug Des., 6(6):569-84; Helene, C., et al., 1992, Ann, N.Y. Acad. Sci., 660:27-36; and Maher, L. J., 1992, Bioassays 14(12):807-15). Nucleic acid molecules used in triple helix formation for the inhibition of transcription are generally single stranded deoxyribonucleotides. The base composition must be designed to promote triple helix formation via Hoogsteen base pairing rules, which generally require sizeable stretches of either purines or pyrimidines to be present on one strand of a duplex. Nucleotide sequences may be pyrimidine-based, which will result in TAT and CGC+ triplets across the three associated strands of the resulting triple helix. The pyrimidine-rich molecules provide base complementarity to a purine-rich region of a single strand of the duplex in a parallel orientation to that strand. In addition, nucleic acid molecules may be chosen that are purine-rich, for example, containing a stretch of G residues. These molecules will form a triple helix with a DNA duplex that is rich in GC pairs, in which the majority of the purine residues are located on a single strand of the targeted duplex, resulting in GGC triplets across the three strands in the triplex.

Alternatively, the potential sequences that can be targeted for triple helix formation may be increased by creating a so called "switchback" nucleic acid molecule. Switchback molecules are synthesized in an alternating 5'-3', 3'-5' manner, such that they base pair with first one strand of a duplex and then the other, eliminating the necessity for a sizeable stretch of either purines or pyrimidines to be present on one strand of a duplex.

Another technique for inhibiting the expression of a gene involves the use of RNA for induction of RNA interference (RNAi), using double stranded

(dsRNA) (Fire *et al.*, *Nature 391*: 806-811. 1998) or small interfering RNA (siRNA) sequences (Elbashir et al, Nature 411, 494 - 498 (2001)); Yu *et al.*, *Proc Natl Acad Sci U S A*. 99:6047-52 (2002). "RNAi" is the process by which dsRNA induces homology-dependent degradation of complimentary mRNA. The presence of dsRNA in cells triggers the RNAi response though a mechanism that has yet to be fully characterized. In one embodiment, a synthetic antisense nucleic acid molecule is hybridized by complementary base pairing with a "sense" ribonucleic acid to form a double stranded RNA. The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme. The dsRNA antisense and sense nucleic acid molecules are provided that correspond to at least about 20, 25, 50, 100, 250 or 500 nucleotides or an entire Prox-1 coding strand, or to only a portion thereof. In an alternative embodiment, the siRNAs are 30 nucleotides or less in length, and more preferably 21- to 23-nucleotides, with characteristic 2- to 3- nucleotide 3'-overhanging ends, which are generated by ribonuclease III cleavage from longer dsRNAs. (*See e.g.* Tuschl T. *Nat Biotechnol.* 20:446-48. 2002). At notably higher concentrations single stranded 21 nucleotide RNA molecules have been also shown to function as siRNAs (*i.e.*, enter the RNAi pathway and specifically target mRNA for degradation in mammalian cells (Martinez et al., Cell 110, 563-574, 2002). Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex (Elbashir et al., 2001, Genes Dev., 15, 188).

Intracellular transcription of small RNA molecules can be achieved by cloning the siRNA templates into RNA polymerase III (Pol III) transcription units, which normally encode the small nuclear RNA (snRNA) U6 or the human RNAse P RNA H1. Two approaches can be used to express siRNAs: in one embodiment, sense and antisense strands constituting the siRNA duplex are transcribed using constructs with individual promoters (Lee, *et al. Nat. Biotechnol.* 20, 500-505. 2002); in an alternative embodiment, siRNAs are expressed as stem-loop hairpin RNA structures that give rise to siRNAs after intracellular processing (Brummelkamp *et al. Science* 296:550-553. 2002, herein incorporated by reference). Alternatively, a stem loop hairpin can be expressed within an unrelated Pol II transcribed mRNA transcript. A stem-loop hairpin designed to contain the siRNA sequence also contains conserved microRNA sequences within the loop and stem regions, thus resembling a natural

precursor mRNA structure. Subsequently, the precursor can be processed by the cellular RNAi components to yield mature, functional siRNA/miRNA. (See, generally, Zeng et al., Mol Cell 9, 1327-1333 (2002); Hutvagner et al., Science 297, 2056-2060 (2002); Kawasake et al., Nature 423, 838-842 (2003)).

RNAi has been studied in a variety of systems. Work in Drosophila embryonic lysates (Elbashir et al., 2001, EMBO J, 20, 6877) has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. Twenty-one nucleotide siRNA duplexes are most active when containing two nucleotide 3'-overhangs. Replacing the 3'-overhanging segments of a 21-mer siRNA duplex having 2 nucleotide 3' overhangs with deoxyribonucleotides has no adverse effect on RNAi activity, while, replacing up to 4 nucleotides on each end of the siRNA with deoxyribonucleotides may be well tolerated. Complete substitution with deoxyribonucleotides results in no RNAi activity (Elbashir et al., 2001, EMBO J., 20, 6877).

Furthermore, complete substitution of one or both siRNA strands with 2'-deoxy (2'-H) or 2'-O-methyl nucleotides results in no RNAi activity, whereas substitution of the 3'-terminal siRNA overhang nucleotides with deoxy nucleotides (2'-H) is tolerated. Single mismatch sequences in the center of the siRNA duplex may abolish RNAi activity. In addition, studies indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end (Elbashir et al., 2001, EMBO J, 20, 6877). Other studies indicate that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA (Nykanen et al., 2001, Cell, 107, 309).

The dsRNA/siRNA is most commonly administered by annealing sense and antisense RNA strands *in vitro* before delivery to the organism. In an alternate embodiment, RNAi may be carried out by administering sense and antisense nucleic acids of the invention in the same solution without annealing prior to administration, and may even be performed by administering the nucleic acids in separate vehicles within a very close timeframe.

Genetic control can also be achieved through the design of novel transcription factors for modulating expression of the gene of interest in native cells and animals. For example, the Cys2-His2 zinc finger proteins, which bind DNA via their zinc finger domains, have been shown to be amenable to structural changes that lead to the recognition of different target sequences. These artificial zinc finger proteins recognize specific target sites with high affinity and low dissociation constants, and are able to act as gene switches to modulate gene expression. Knowledge of the particular target sequence of the present invention facilitates the engineering of zinc finger proteins specific for the target sequence using known methods such as a combination of structure-based modeling and screening of phage display libraries (Segal et al., (1999) Proc Natl Acad Sci USA 96:2758-2763; Liu et al., (1997) Proc Natl Acad Sci USA 94:5525-30; Greisman and Pabo (1997) Science 275:657-61; Choo et al., (1997) J Mol Biol 273:525-32). Each zinc finger domain usually recognizes three or more base pairs. Since a recognition sequence of 18 base pairs is generally sufficient in length to render it unique in any known genome, a zinc finger protein consisting of 6 tandem repeats of zinc fingers would be expected to ensure specificity for a particular sequence (Segal et al., (1999) Proc Natl Acad Sci USA 96:2758-2763). The artificial zinc finger repeats, designed based on target sequences, are fused to activation or repression domains to promote or suppress gene expression (Liu et al., (1997) Proc Natl Acad Sci USA 94:5525-30). Alternatively, the zinc finger domains can be fused to the TATA box-binding factor (TBP) with varying lengths of linker region between the zinc finger peptide and the TBP to create either transcriptional activators or repressors (Kim et al., (1997) Proc Natl Acad Sci USA 94:3616-3620). Such proteins, and polynucleotides that encode them, have utility for modulating expression *in vivo* in both native cells, animals and humans. The novel transcription factor can be delivered to the target cells by transfecting constructs that express the transcription factor (gene therapy), or by introducing the protein. Engineered zinc finger proteins can also be designed to bind RNA sequences for use in therapeutics as alternatives to antisense or catalytic RNA methods (McColl et al., (1999) Proc Natl Acad Sci USA 96:9521-6; Wu et al., (1995) Proc Natl Acad Sci USA 92:344-348).

Inactivation of Prox-1 function can also be accomplished using an overexpressed dominant negative form of Prox-1. As used herein a "dominant negative protein" is a mutant form of a protein which has the property of inhibiting the function of the endogenous, wild type form of the protein which corresponds to the mutant protein. Typically, dominant negative proteins have amino acid substitutions or are truncated forms of the wild type protein. The mutation may be in a substrate-binding domain (or DNA binding domain), a catalytic domain, or a cellular localization domain. For instance, a dominant negative form of Prox-1 may include a mutant truncated with respect to the DNA binding domain or transactivation domain. Disruption of the DNA binding domain entails truncation of the protein to exclude amino acids 572-634 of SEQ ID NO. 3, based on homology to Prospero (*Drosophila*). Disruption of the transactivation domain entails the deletion of amino acids 635-737. Other dominant negatives may include truncated forms of Prox-1 lacking the last 60 amino acids or the first 575 amino acids. Preferably, the mutant polypeptide will be overproduced. Point mutations can be made that have such an effect. In addition, fusion of different polypeptides of various lengths to the terminus of a protein can yield dominant negative mutants. General strategies for making dominant negative mutants are described in Herskowitz, Nature (1987) 329:219-222.

Anti-sense RNA and DNA molecules, ribozymes, RNAi, triple helix polynucleotides, and novel transcription factors can be prepared by any method known in the art for the synthesis of DNA and RNA molecules. These include techniques for chemically synthesizing oligodeoxyribonucleotides well known in the art including, but not limited to, solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding the antisense RNA molecule. Such DNA sequences may be incorporated into a wide variety of vectors which incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly, depending on the promoter used, can be introduced stably or transiently into cells.

B. Gene Therapy

As described n detail in the preceding section, a variety of genetic manipulations to achieve modulation of Prox-1 protein expression or activity are

contemplated. Additionally, where administration of proteins is contemplated, such as zinc finger proteins targeted to Prox-1, administration of a gene therapy vector to cause the protein of interest to be produced *in vivo* also is contemplated. Where inhibition of proteins is contemplated (e.g., through use of antibodies or small molecule inhibitors), inhibition of protein expression *in vivo* by genetic techniques, such as knock-out techniques or anti-sense therapy, is contemplated.

It is now widely recognized that DNA may be introduced into a cell using a variety of viral vectors. Exemplary vectors that have been described in the literature include replication-deficient retroviral vectors, including but not limited to lentivirus vectors (Kim et al., J. Virol., 72(1): 811-816 (1998); Kingsman & Johnson, Scrip Magazine, October, 1998, pp. 43-46.); adenoviral (*see*, for example, U.S. Patent No. 5,824,544; U.S. Patent No. 5,707,618; U.S. Patent No. 5,792,453; U.S. Patent No. 5,693,509; U.S. Patent No. 5,670,488; U.S. Patent No. 5,585,362; Quantin et al., Proc. Natl. Acad. Sci. USA, 89: 2581-2584 (1992); Stratford-Perricadet et al., J. Clin. Invest., 90: 626-630 (1992); and Rosenfeld et al., Cell, 68: 143-155 (1992)), retroviral (*see*, for example, U.S. Patent No. 5,888,502; U.S. Patent No. 5,830,725; U.S. Patent No. 5,770,414; U.S. Patent No. 5,686,278; U.S. Patent No. 4,861,719), adeno-associated viral (*see*, for example, U.S. Patent No. 5,474,935; U.S. Patent No. 5,139,941; U.S. Patent No. 5,622,856; U.S. Patent No. 5,658,776; U.S. Patent No. 5,773,289; U.S. Patent No. 5,789,390; U.S. Patent No. 5,834,441; U.S. Patent No. 5,863,541; U.S. Patent No. 5,851,521; U.S. Patent No. 5,252,479; Gnatenko et al., J. Investig. Med., 45: 87-98 (1997), an adenoviral-adenoassociated viral hybrid (*see*, for example, U.S. Patent No. 5,856,152) or a vaccinia viral or a herpesviral (*see*, for example, U.S. Patent No. 5,879,934; U.S. Patent No. 5,849,571; U.S. Patent No. 5,830,727; U.S. Patent No. 5,661,033; U.S. Patent No. 5,328,688); Lipofectin-mediated gene transfer (BRL); liposomal vectors (See, e.g., U.S. Patent No. 5,631,237 (Liposomes comprising Sendai virus proteins)) ; and combinations thereof. All of the foregoing documents are incorporated herein by reference in the entirety. Replication-deficient adenoviral vectors and adeno-associated viral vectors constitute preferred embodiments.

In embodiments employing a viral vector, preferred polynucleotides include a suitable promoter and polyadenylation sequence to promote expression in

the target tissue of interest. For many applications of the present invention, suitable promoters/enhancers for mammalian cell expression include, e.g., cytomegalovirus promoter/enhancer (Lehner et al., J. Clin. Microbiol., 29:2494-2502 (1991); Boshart et al., Cell, 41:521-530 (1985)); Rous sarcoma virus promoter (Davis et al., Hum. Gene Ther., 4:151 (1993)); simian virus 40 promoter, long terminal repeat (LTR) of retroviruses, keratin 14 promoter, and myosin heavy chain promoter.

In other embodiments, non-viral delivery is contemplated. These include calcium phosphate precipitation (Graham and Van Der Eb, *Virology*, 52:456-467 (1973); Chen and Okayama, *Mol. Cell Biol.*, 7:2745-2752, (1987); Rippe, *et al.*, *Mol. Cell Biol.*, 10:689-695 (1990)), DEAE-dextran (Gopal, *Mol. Cell Biol.*, 5:1188-1190 (1985)), electroporation (Tur-Kaspa, *et al.*, *Mol. Cell Biol.*, 6:716-718, (1986); Potter, *et al.*, *Proc. Nat. Acad. Sci. USA*, 81:7161-7165, (1984)), direct microinjection (Harland and Weintraub, *J. Cell Biol.*, 101:1094-1099 (1985)), DNA-loaded liposomes (Nicolau and Sene, *Biochim. Biophys. Acta*, 721:185-190 (1982); Fraley, *et al.*, *Proc. Natl. Acad. Sci. USA*, 76:3348-3352 (1979); Felgner, *Sci. Am.*, 276(6):102-6 (1997); Felgner, *Hum. Gene Ther.*, 7(15):1791-3, (1996)), cell sonication (Fechheimer, *et al.*, *Proc. Natl. Acad. Sci. USA*, 84:8463-8467 (1987)), gene bombardment using high velocity microprojectiles (Yang, *et al.*, *Proc. Natl. Acad. Sci. USA*, 87:9568-9572 (1990)), and receptor-mediated transfection (Wu and Wu, *J. Biol. Chem.*, 262:4429-4432 (1987); Wu and Wu, *Biochemistry*, 27:887-892 (1988); Wu and Wu, *Adv. Drug Delivery Rev.*, 12:159-167 (1993)).

In a particular embodiment of the invention, the expression construct (or indeed the peptides discussed above) may be entrapped in a liposome. Liposomes are vesicular structures characterized by a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh and Bachhawat, "In Liver Diseases, Targeted Diagnosis And Therapy Using Specific Receptors And Ligands," Wu, G., Wu, C., ed., New York: Marcel Dekker, pp. 87-104 (1991)). The addition of DNA to cationic liposomes causes a topological transition from liposomes to optically birefringent

liquid-crystalline condensed globules (Radler, *et al.*, *Science*, 275(5301):810-4, (1997)). These DNA-lipid complexes are potential non-viral vectors for use in gene therapy and delivery.

Liposome-mediated nucleic acid delivery and expression of foreign DNA *in vitro* has been very successful. Also contemplated in the present invention are various commercial approaches involving "lipofection" technology. In certain embodiments of the invention, the liposome may be complexed with a hemagglutinating virus (HVJ). This has been shown to facilitate fusion with the cell membrane and promote cell entry of liposome-encapsulated DNA (Kaneda, *et al.*, *Science*, 243:375-378 (1989)). In other embodiments, the liposome may be complexed or employed in conjunction with nuclear nonhistone chromosomal proteins (HMG-1) (Kato, *et al.*, *J. Biol. Chem.*, 266:3361-3364 (1991)). In yet further embodiments, the liposome may be complexed or employed in conjunction with both HVJ and HMG-1. In that such expression constructs have been successfully employed in transfer and expression of nucleic acid *in vitro* and *in vivo*, then they are applicable for the present invention.

Other vector delivery systems that can be employed to deliver a nucleic acid encoding a therapeutic gene into cells include receptor-mediated delivery vehicles. These take advantage of the selective uptake of macromolecules by receptor-mediated endocytosis in almost all eukaryotic cells. Because of the cell type-specific distribution of various receptors, the delivery can be highly specific (Wu and Wu (1993), *supra*).

Receptor-mediated gene targeting vehicles generally consist of two components: a cell receptor-specific ligand and a DNA-binding agent. Several ligands have been used for receptor-mediated gene transfer. The most extensively characterized ligands are asialoorosomucoid (ASOR) (Wu and Wu (1987), *supra*) and transferrin (Wagner, *et al.*, *Proc. Nat'l. Acad Sci. USA*, 87(9):3410-3414 (1990)). Recently, a synthetic neoglycoprotein, which recognizes the same receptor as ASOR, has been used as a gene delivery vehicle (Ferkol, *et al.*, *FASEB J.*, 7:1081-1091 (1993); Perales, *et al.*, *Proc. Natl. Acad. Sci., USA* 91:4086-4090 (1994)) and epidermal growth factor (EGF) has also been used to deliver genes to squamous carcinoma cells (Myers, EPO 0273085).

In other embodiments, the delivery vehicle may comprise a ligand and a liposome. For example, Nicolau, *et al., Methods Enzymol.*, 149:157-176 (1987) employed lactosyl-ceramide, a galactose-terminal asialganglioside, incorporated into liposomes and observed an increase in the uptake of the insulin gene by hepatocytes. Thus, it is feasible that a nucleic acid encoding a therapeutic gene also may be specifically delivered into a particular cell type by any number of receptor-ligand systems with or without liposomes.

In another embodiment of the invention, the expression construct may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above that physically or chemically permeabilize the cell membrane. This is applicable particularly for transfer *in vitro*, however, it may be applied for *in vivo* use as well. Dubensky, *et al.*, *Proc. Nat. Acad. Sci. USA*, 81:7529-7533 (1984) successfully injected polyomavirus DNA in the form of $CaPO_4$ precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Neshif, *Proc. Nat. Acad. Sci. USA*, 83:9551-9555 (1986) also demonstrated that direct intraperitoneal injection of $CaPO_4$ precipitated plasmids results in expression of the transfected genes.

Another embodiment of the invention for transferring a naked DNA expression construct into cells may involve particle bombardment. This method depends on the ability to accelerate DNA coated microprojectiles to a high velocity allowing them to pierce cell membranes and enter cells without killing them (Klein, *et al.*, *Nature*, 327:70-73 (1987)). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang, *et al.*, *Proc. Natl. Acad. Sci USA*, 87:9568-9572 (1990)). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

Well-known techniques exist for gene delivery to *in vivo* and *ex vivo* situations. For viral vectors, one generally will prepare a viral vector stock. Depending on the type of virus and the titer attainable, one will deliver 1×10^4, 1×10^5, 1×10^6, 1×10^7, 1×10^8, 1×10^9, 1×10^{10}, 1×10^{11} or 1×10^{12} infectious particles to the patient. Similar figures may be extrapolated for liposomal or other non-viral

formulations by comparing relative uptake efficiencies. Formulation as a pharmaceutically acceptable composition is discussed below.

Various routes are contemplated for various tumor types. For practically any tumor, systemic delivery is contemplated. This will prove especially important for attacking microscopic or metastatic cancer. Where discrete tumor mass may be identified, a variety of direct, local and regional approaches may be taken. For example, the tumor may be directly injected with the expression vector or protein. A tumor bed may be treated prior to, during or after resection. Following resection, one generally will deliver the vector by a catheter left in place following surgery. One may utilize the tumor vasculature to introduce the vector into the tumor by injecting a supporting vein or artery. A more distal blood supply route also may be utilized.

In an *ex vivo* embodiment, cells from the patient are removed and maintained outside the body for at least some period of time. During this period, a therapy is delivered, after which the cells are reintroduced into the patient; preferably, any tumor cells in the sample have been killed.

C. Antibodies Immunoreactive with Prox-1 Protein

In another aspect, the present invention contemplates an antibody that is immunoreactive with a Prox-1 protein molecule of the present invention, or any portion thereof. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments and fragments produced by a Fab expression library, bifunctional/bispecific antibodies, humanized antibodies, CDR grafted antibodies, human antibodies and antibodies which include portions of CDR sequences specific for Prox-1 protein. The antibodies are useful as diagnostic reagents for measuring Prox-1 expression in a biological sample (*e.g.*, a biopsy of colon tissue), and are useful for binding to Prox-1 protein to inhibit Prox-1 activity where the antibodies are delivered into cells.

Neutralizing antibodies, i.e., those which may suppress Prox-1 expression, are especially preferred for therapeutic embodiments. In a preferred embodiment, an antibody is a monoclonal antibody. The invention provides for a pharmaceutical composition comprising a therapeutically effective amount of an antibody directed against Prox-1 protein. The antibody may bind to and neutralize the

apoptotic effects of the Prox-1 protein. The antibody may be formulated with a pharmaceutically acceptable adjuvant. Means for preparing and characterizing antibodies are well known in the art (see, e.g., Harlow and Lane, ANTIBODIES: A LABORATORY MANUAL, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1988).

Briefly, a polyclonal antibody is prepared by immunizing an animal with an immunogen comprising a polypeptide of the present invention and collecting antisera from that immunized animal. A wide range of animal species can be used for the production of antisera. Typically an animal used for production of anti-antisera is a non-human animal including rabbits, mice, rats, hamsters, goat, sheep, pigs or horses. Because of the relatively large blood volume of rabbits, a rabbit is a preferred choice for production of polyclonal antibodies.

Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include but are not limited to Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, and dinitrophenol. BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are potentially useful human adjuvants.

Antibodies, both polyclonal and monoclonal, specific for isoforms of antigen may be prepared using conventional immunization techniques, as will be generally known to those of skill in the art. As used herein, the term "specific for" is intended to mean that the variable regions of the antibodies recognize and bind Prox-1 protein and are capable of distinguishing Prox-1 protein from other antigens, for example other secreted proapoptotic factors. A composition containing antigenic epitopes of the compounds of the present invention can be used to immunize one or more experimental animals, such as a rabbit or mouse, which will then proceed to produce specific antibodies against the compounds of the present invention. Polyclonal antisera may be obtained, after allowing time for antibody generation, simply by bleeding the animal and preparing serum samples from the whole blood.

Monoclonal antibodies to Prox-1 protein may be prepared using any technique which provides for the production of antibody molecules by continuous cell

lines in culture. These include but are not limited to the hybridoma technique originally described by Koehler and Milstein (Nature 256: 495-497, 1975), the human B-cell hybridoma technique (Kosbor *et al.*, Immunol Today 4:72, 1983 ; Cote *et al.*, Proc Natl Acad Sci 80: 2026-2030, 1983) and the EBV-hybridoma technique (Cole *et al.*, Monoclonal Antibodies and Cancer Therapy, Alan R Liss Inc, New York N.Y., pp 77-96, (1985).

When the hybridoma technique is employed, myeloma cell lines may be used. Such cell lines suited for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). For example, where the immunized animal is a mouse, one may use P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XX0 Bul; for rats, one may use R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210; and U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6 are all useful in connection with cell fusions. It should be noted that the hybridomas and cell lines produced by such techniques for producing the monoclonal antibodies are contemplated to be novel compositions of the present invention. An exemplary method for producing monoclonal antibodies against Prox-1 is provided in Example 1. Those of skill in the art will appreciate that such a method may be modified using techniques well known to those of skill in the art and still produce antibodies within the scope of the present invention.

In addition to the production of monoclonal antibodies, techniques developed for the production of "chimeric antibodies", the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity can be used (Morrison *et al.*, Proc Natl Acad Sci 81: 6851-6855, 1984 ; Neuberger *et al.*, Nature 312: 604-608, 1984; Takeda *et al.*, Nature 314: 452-454; 1985). Alternatively, techniques described for the production of single chain antibodies (U.S. Pat. No. 4,946,778) can be adapted to produce Prox-1 protein-specific single chain antibodies.

Antibodies may also be produced by inducing *in vivo* production in the lymphocyte population or by screening recombinant immunoglobulin libraries or

panels of highly specific binding reagents as disclosed in Orlandi et al (Proc Natl Acad Sci 86: 3833-3837; 1989), and Winter G and Milstein C (Nature 349: 293-299, 1991).

Fully human antibodies relate to antibody molecules in which essentially the entire sequences of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies," or "fully human antibodies" herein. Human monoclonal antibodies can be prepared by the trioma technique; the human B-cell hybridoma technique (see Kozbor, *et al., Immunol Today* 4: 72 (1983)) and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole, *et al.,* 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized in the practice of the present invention and may be produced by using human hybridomas (see Cote, et al., *Proc Natl Acad Sci USA* 80: 2026-2030 (1983)) or by transforming human B-cells with Epstein Barr Virus *in vitro* (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

In addition, human antibodies can also be produced using additional techniques, including phage display libraries (Hoogenboom and Winter, *J. Mol. Biol.* 227:381 (1991); Marks *et al., J. Mol. Biol.* 222:581 (1991)). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in Marks et al. (Bio/Technology 10, 779-783 (1992)); Lonberg *et al.* (*Nature* 368 856-859 (1994)); Morrison (*Nature* 368:812-13 (1994)); Fishwild et al,(Nature Biotechnology 14, 845-51 (1996)); Neuberger (*Nature Biotechnology* 14:826 (1996)); and Lonberg and Huszar (*Intern. Rev. Immunol.* 13:65-93 (1995)).

Human antibodies may additionally be produced using transgenic nonhuman animals which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (See

PCT publication WO94/02602). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins are inserted into the host's genome. The human genes are incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full complement of the modifications. The preferred embodiment of such a nonhuman animal is a mouse, and is termed the Xenomouse™ as disclosed in PCT publications WO 96/33735 and WO 96/34096. This animal produces B cells which secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the immunoglobulins with human variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv molecules.

An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No. 5,939,598. It can be obtained by a method including deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable marker; and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells contain the gene encoding the selectable marker.

Antibodies as described herein are useful in standard immunochemical procedures, such as ELISA, radioimmuno assays, and Western blot methods and in immunohistochemical procedures such as tissue staining, as well as in other procedures which may utilize antibodies specific to Prox-1 protein -related antigen epitopes. Additionally, it is proposed that monoclonal antibodies specific to the

particular Prox-1 protein of different species may be utilized in other useful applications.

In general, both polyclonal and monoclonal antibodies against Prox-1 protein may be used in a variety of embodiments. In certain aspects, the antibodies may be employed for therapeutic purposes in which the inhibition of Prox-1 protein activity is desired (e.g., to reduce apoptosis in neuronal cells). Antibodies may be used to block Prox-1 protein action.

Antibodies of the present invention also may prove useful in diagnostic purposes in order, for example, to detect increases or decreases in Prox-1 protein in tissue samples including samples for sites of inflammation, or fluid samples including blood serum, plasma and exudate samples. Additional aspects will employ the antibodies of the present invention in antibody cloning protocols to obtain cDNAs or genes encoding other Prox-1 protein. They may also be used in inhibition studies to analyze the effects of Prox-1 related peptides in cells or animals. Anti- Prox-1 protein antibodies will also be useful in immunolocalization studies to analyze the distribution of Prox-1 protein during various cellular events, for example, to determine the cellular or tissue-specific distribution of Prox-1 protein polypeptides under different points in the cell cycle. A particularly useful application of such antibodies is in purifying native or recombinant Prox-1 protein, for example, using an antibody affinity column. The operation of all such immunological techniques will be known to those of skill in the art in light of the present disclosure.

D. Assaying for Other Modulators of Prox-1 Activity and/or Expression

In some situations, it may be desirable to identify molecules that are modulators, *i.e.*, agonists or antagonists, of the activity of Prox-1 protein. Natural or synthetic molecules that modulate Prox-1 protein may be identified using one or more screening assays, such as those described herein. Such molecules may be administered either in an *ex vivo* manner, or in an *in vivo* manner by injection, or by oral delivery, implantation device or the like.

"Test molecule(s)" refers to the molecule(s) that is/are under evaluation for the ability to modulate (i.e., increase or decrease) the activity of Prox-1 protein. Most commonly, a molecule that modulates Prox-1 activity will interact directly with

Prox-1. However, it is also contemplated that a molecule may also modulate Prox-1 protein activity indirectly, such as by affecting Prox-1 gene expression, or by binding to a Prox-1 binding partner. In one embodiment, a test molecule will bind to a Prox-1 protein with an affinity constant of at least about 10^{-6} M, preferably about 10^{-8} M, more preferably about 10^{-9} M, and even more preferably about 10^{-10} M.

Methods for identifying compounds which interact with Prox-1 protein are encompassed by the present invention. In certain embodiments, a Prox-1 protein is incubated with a test molecule under conditions which permit the interaction of the test molecule with a Prox-1 protein, and the extent of the interaction can be measured. The test molecule(s) can be screened in a substantially purified form or in a crude mixture.

In certain embodiments, a Prox-1 protein agonist or antagonist may be a protein, peptide, carbohydrate, lipid or small molecular weight molecule which interacts with Prox-1 to regulate its activity. Molecules which regulate Prox-1 expression include nucleic acids which are complementary to nucleic acids encoding a Prox-1 protein, or are complementary to nucleic acid sequences which direct or control the expression of Prox-1 protein, and which act as anti-sense regulators of expression.

Once a set of test molecules has been identified as interacting with Prox-1 protein, the molecules may be further evaluated for their ability to increase or decrease Prox-1 activity. The measurement of the interaction of test molecules with Prox-1 may be carried out in several formats, including solution-phase assays and immunoassays. In general, test molecules are incubated with Prox-1 for a specified period of time, and Prox-1 protein activity is determined by one or more assays for measuring biological activity.

In the event that Prox-1 displays biological activity through an interaction with a binding partner, a variety of *in vitro* assays may be used to measure the binding of Prox-1 to the corresponding binding partner. These assays may be used to screen test molecules for their ability to increase or decrease the rate and/or the extent of binding of Prox-1 to its binding partner. In one assay, a Prox-1 polypeptide is immobilized in the wells of a microtiter plate. Radiolabeled Prox-1

binding partner and the test molecule(s) can then be added either one at a time (in either order) or simultaneously to the wells. After incubation, the wells can be washed and counted (using a scintillation counter) for radioactivity to determine the extent to which the binding partner bound to Prox-1 polypeptide. Typically, the molecules will be tested over a range of concentrations, and a series of control wells lacking one or more elements of the test assays can be used for accuracy in the evaluation of the results. An alternative to this method involves reversing the "positions" of the proteins, *i.e.*, immobilizing Prox-1 binding partner to the microtiter plate wells, incubating with the test molecule and radiolabeled Prox-1 polypeptide, and determining the extent of Prox-1 polypeptide binding. See, for example, chapter 18, *Current Protocols in Molecular Biology*, Ausubel *et al.*, eds., John Wiley & Sons, New York, NY (1995).

As an alternative to radiolabeling, Prox-1 protein or its binding partner may be conjugated to biotin and the presence of biotinylated protein can then be detected using streptavidin linked to an enzyme, such as horseradish peroxidase (HRP) or alkaline phosphatase (AP), that can be detected colorometrically or by fluorescent tagging of streptavidin. An antibody directed to Prox-1 or to a Prox-1 binding partner and conjugated to biotin may also be used and can be detected after incubation with enzyme-linked streptavidin linked to AP or HRP.

A Prox-1 protein or Prox-1 binding partner can also be immobilized by attachment to agarose beads, acrylic beads or other types of such inert solid phase substrates. The substrate-protein complex can be placed in a solution containing the complementary protein and the test compound. After incubation the beads can be precipitated by centrifugation, and the amount of binding between Prox-1 protein and its binding partner can be assessed using the methods described herein. Alternatively, the substrate-protein complex can be immobilized in a column, and the test molecule and complementary protein are passed through the column. The formation of a complex between an Prox-1 protein and its binding partner can then be assessed using any of the techniques set forth herein, *i.e.*, radiolabeling, antibody binding or the like.

Another *in vitro* assay that is useful for identifying a test molecule which increases or decreases the formation of a complex between Prox-1 and a Prox-1 binding partner is a surface plasmon resonance detector system such as the BIAcore

assay system (Pharmacia, Piscataway, NJ). The BIAcore system may be carried out using the manufacturer's protocol. This assay essentially involves the covalent binding of either Prox-1 or a Prox-1 binding partner to a dextran-coated sensor chip which is located in a detector. The test compound and the other complementary protein can then be injected, either simultaneously or sequentially, into the chamber containing the sensor chip. The amount of complementary protein that binds can be assessed based on the change in molecular mass which is physically associated with the dextran-coated side of the sensor chip; the change in molecular mass can be measured by the detector system.

In some cases, it may be desirable to evaluate two or more test compounds together for their ability to increase or decrease the formation of a complex between Prox-1 polypeptide and a Prox-1 binding partner. In these cases, the assays set forth herein can be readily modified by adding such additional test compound(s) either simultaneous with, or subsequent to, the first test compound. The remainder of the steps in the assay are as set forth herein.

In vitro assays such as those described herein may be used advantageously to screen large numbers of compounds for effects on complex formation by Prox-1 polypeptide and a Prox-1 binding partner. The assays may be automated to screen compounds generated in phage display, synthetic peptide, and chemical synthesis libraries.

Compounds which increase or decrease the formation of a complex between a Prox-1 polypeptide and a Prox-1 binding partner may also be screened in cell culture using cells and cell lines expressing either Prox-1 polypeptide or a Prox-1 binding partner. Cells and cell lines may be obtained from any mammal. The binding of a Prox-1 protein to cells expressing a Prox-1 binding partner at the surface is evaluated in the presence or absence of test molecules, and the extent of binding may be determined by, for example, flow cytometry using a biotinylated antibody to a Prox-1 binding partner. Cell culture assays can be used advantageously to further evaluate compounds that score positive in protein binding assays described herein.

Cell cultures can also be used to screen the impact of a drug candidate. For example, drug candidates may decrease or increase the expression of the Prox-1

like gene. In certain embodiments, the amount of Prox-1 protein that is produced may be measured after exposure of the cell culture to the drug candidate. In certain embodiments, one may detect the actual impact of the drug candidate on the cell culture. For example, the overexpression of a particular gene may have a particular impact on the cell culture. In such cases, one may test a drug candidate's ability to increase or decrease the expression of the gene or its ability to prevent or inhibit a particular impact on the cell culture. In other examples, the production of a particular metabolic product such as a fragment of a polypeptide may result in, or be associated with, a disease or pathological condition. In such cases, one may test a drug candidate's ability to decrease the production of such a metabolic product in a cell culture.

E. Internalizing Proteins

The *tat* protein sequence (from HIV) can be used to internalize proteins into a cell. See *e.g.*, Falwell *et al.*, *Proc. Natl. Acad. Sci. USA*, 91:664-668 (1994). For example, an 11 amino acid sequence (YGRKKRRQRRR; SEQ ID NO: 46) of the HIV tat protein (termed the "protein transduction domain", or TAT PDT) has been described as mediating delivery across the cytoplasmic membrane and the nuclear membrane of a cell. See Schwarze *et al.*, *Science*, 285:1569-1572 (1999); and Nagahara *et al.*, *Nature Medicine*, 4:1449-1452 (1998). In these procedures, FITC-constructs are prepared which bind to cells as observed by fluorescence-activated cell sorting (FACS) analysis, and these constructs penetrate tissues after i.p. adminstration. Next, tat-bgal fusion proteins are constructed. Cells treated with this construct demonstrate b-gal activity. Following injection, a number of tissues, including liver, kidney, lung, heart and brain tissue, have been found to demonstrate expression using these procedures. It is believed that these constructions underwent some degree of unfolding in order to enter the cell; as such, refolding may be required after entering the cell.

It will thus be appreciated that the tat protein sequence may be used to internalize a desired protein or polypeptide into a cell. For example, using the *tat* protein sequence, Prox-1 antagonist (such as an anti-Prox-1 binding agent, small molecule, or antisense oligonucleotide) can be administered intracellularly to inhibit

the activity of a Prox-1 molecule. See also, Strauss, E., *Science*, 285:1466-1467 (1999).

F. Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptides or compounds with which they interact (agonists, antagonists, inhibitors, peptidomimetics, binding partners, etc.). By creating such analogs, it is possible to fashion drugs which are more active or stable than the natural molecules, which have different susceptibility to alteration or which may affect the function of various other molecules. In one approach, one generates a three-dimensional structure for Prox-1 protein or a fragment thereof. This is accomplished by x-ray crystallography, computer modeling or by a combination of both approaches. An alternative approach, "alanine scan," involves the random replacement of residues throughout molecule with alanine, and the resulting affect on function determined.

It also is possible to isolate a specific antibody, selected by a functional assay, and then solve its crystal structure. In principle, this approach yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of anti-idiotype would be expected to be an analog of the original antigen. The anti-idiotype could then be used to identify and isolate peptides from banks of chemically- or biologically-produced peptides. Selected peptides would then serve as the pharmacore. Anti-idiotypes may be generated using the methods described herein for producing antibodies, using an antibody as the antigen.

Thus, one may design drugs which have activity as stimulators, inhibitors, agonists, antagonists of Prox-1 protein or molecules affected by Prox-1 protein function. Such rational drug design may start with lead compounds identified by the present invention. By virtue of the availability of cloned Prox-1 protein sequences, sufficient amounts of the related proteins can be produced to perform crystallographic studies. In addition, knowledge of the polypeptide sequences permits computer employed predictions of structure-function relationships.

G. Therapeutic Methods

As discussed herein, polynucleotides or modulators of Prox-1 (including inhibitors of Prox-1) are administered to treat cancer. Therapeutic compositions can be administered in therapeutically effective dosages alone or in combination with adjuvant cancer therapy such as surgery, chemotherapy, radiotherapy, thermotherapy, and laser therapy, and may provide a beneficial effect, e.g. reducing tumor size, slowing rate of tumor growth, inhibiting metastasis, or otherwise improving overall clinical condition, without necessarily eradicating the cancer.

The composition can also be administered in therapeutically effective amounts as a portion of an anti-cancer cocktail. An anti-cancer cocktail is a mixture of the polypeptide or modulator of the invention with one or more anti-cancer drugs in addition to a pharmaceutically acceptable carrier for delivery. Any anti-cancer drugs can be used as a treatment in combination with the polypeptide or modulator of the invention, including: Actinomycin D, Aminoglutethimide, Asparaginase, Bleomycin, Busulfan, Carboplatin, Carmustine, Chlorambucil, Cisplatin (cis-DDP), Cyclophosphamide, Cytarabine HCl (Cytosine arabinoside), Dacarbazine, Dactinomycin, Daunorubicin HCl, Doxorubicin HCl, Estramustine phosphate sodium, Etoposide (V16-213), Floxuridine, 5-Fluorouracil (5-Fu), Flutamide, Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alpha-2a, Interferon Alpha-2b, Leuprolide acetate (LHRH-releasing factor analog), Lomustine, Mechlorethamine HCl (nitrogen mustard), Melphalan, Mercaptopurine, Mesna, Methotrexate (MTX), Mitomycin, Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl, Streptozocin, Tamoxifen citrate, Thioguanine, Thiotepa, Vinblastine sulfate, Vincristine sulfate, Amsacrine, Azacitidine, Hexamethylmelamine, Interleukin-2, Mitoguazone, Pentostatin, Semustine, Teniposide, and Vindesine sulfate.

In addition, therapeutic compositions of the invention may be used for prophylactic treatment of cancer. There are hereditary conditions and/or environmental situations (e.g. exposure to carcinogens) known in the art that predispose an individual to developing cancers. Under these circumstances, it may be beneficial to treat these individuals with therapeutically effective doses of compositions of the invention to reduce the risk of developing cancers.

In vitro and *in vivo* models can be used to determine the effective doses of the compositions of the invention for cancer treatment. These *in vitro* models include proliferation and differentiation assays of cultured tumor cells, growth of cultured tumor cells in soft agar (see Freshney, (1987) Culture of Animal Cells: A Manual of Basic Technique, Wily-Liss, New York, NY Ch 18 and Ch 21), tumor systems in nude mice as described in Giovanella et al., J. Natl. Can. Inst., 52: 921-30 (1974), mobility and invasive potential of tumor cells in Boyden Chamber assays as described in Pilkington et al., Anticancer Res., 17: 4107-9 (1997), and angiogenesis assays such as induction of vascularization of the chick chorioallantoic membrane or induction of vascular endothelial cell migration as described in Ribatta et al., Intl. J. Dev. Biol., 40: 1189-97 (1999) and Li et al., Clin. Exp. Metastasis, 17:423-9 (1999) respectively. Suitable tumor cells lines are available, e.g. from American Type Tissue Culture Collection catalogs, and/or are described below.

H. Pharmaceutical Compositions

Purified nucleic acids, antisense molecules, purified protein, antibodies, antagonists, or inhibitors may all be used as pharmaceutical compositions. Delivery of specific molecules for therapeutic purposes in this invention is further described below.

The active compositions of the present invention include classic pharmaceutical preparations. Administration of these compositions according to the present invention will be via any common route so long as the target tissue is available via that route. The pharmaceutical compositions may be introduced into the subject by any conventional method, *e.g.*, by intravenous, intradermal, intramusclar, intramammary, intraperitoneal, intrathecal, intraocular, retrobulbar, intrapulmonary (*e.g.*, term release); by oral, sublingual, nasal, anal, vaginal, or transdermal delivery, or by surgical implantation at a particular site, *e.g.*, embedded under the splenic capsule, brain, or in the cornea. The treatment may consist of a single dose or a plurality of doses over a period of time.

The active compounds may be prepared for administration as solutions of free base or pharmacologically acceptable salts in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions also can be prepared in

glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic

and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions.

For oral administration the active compositions may be incorporated with excipients and used in the form of non-ingestible mouthwashes and dentifrices. A mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an antiseptic wash containing sodium borate, glycerin and potassium bicarbonate. The active ingredient may also be dispersed in dentifrices, including: gels, pastes, powders and slurries. The active ingredient may be added in a therapeutically effective amount to a paste dentifrice that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants.

The compositions of the present invention may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups also can be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The compositions of the present invention may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups also can be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug release capsules and the like. For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration.

In the clinical setting an "effective amount" is an amount sufficient to effect beneficial or desired clinical results. An effective amount can be administered in one or more doses. In terms of treatment, an "effective amount" of polynucleotide, and/or polypeptide is an amount that results in amelioration of symptoms or a prolongation of survival in a patient. The effective amount is generally determined by the physician on a case-by-case basis and is within the skill of one in the art. Several factors are typically taken into account when determining, an appropriate dosage. These factors include age, sex and weight of the patient, the condition being treated, the severity of the condition and the form of the antibody being administered. For instance, in embodiments in which the antibody compositions of the present invention are being therapeutically administered, it is likely the concentration of a single chain antibody need not be as high as that of native antibodies in order to be therapeutically effective. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC50 as determined in cell culture (i.e., the concentration of the test compound which achieves a half-maximal inhibition of the C-proteinase activity). Such information can be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio

between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD50 and ED50. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. See, e.g., Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics," Ch. 1 p.1.Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the C-proteinase inhibiting effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data; for example, the concentration necessary to achieve 50-90% inhibition of the C-proteinase using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration. Refinement of the calculations necessary to determine the appropriate treatment dose is routinely made by those of ordinary skill in the art without undue experimentation, especially in light of the dosage information and assays disclosed herein as well as the pharmacokinetic data observed in animals or human clinical trials. As studies are conducted, further information will emerge regarding appropriate dosage levels and duration of treatment for specific diseases and conditions.

In a preferred embodiment, the present invention is directed at treatment of colon cancer, including colon cancer indicated by the presence of overexpression of Prox-1. A variety of different routes of administration are

contemplated. For example, in the case of a tumor, the discrete tumor mass may be injected. The injections may be single or multiple; where multiple, injections are made at about 1 cm spacings across the accessible surface of the tumor. Alternatively, targeting the tumor vasculature by direct, local or regional intra-arterial injection are contemplated. The lymphatic systems, including regional lymph nodes, present another likely target for delivery. Further, systemic injection may be preferred.

It will be appreciated that the pharmaceutical compositions and treatment methods of the invention may be useful in fields of human medicine and veterinary medicine. Thus the subject to be treated may be a mammal, preferably human or other animal. For veterinary purposes, subjects include for example, farm animals including cows, sheep, pigs, horses and goats, companion animals such as dogs and cats, exotic and/or zoo animals, laboratory animals including mice rats, rabbits, guinea pigs and hamsters; and poultry such as chickens, turkey ducks and geese.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

H. Transgenic Animals

A transgenic animal can be prepared in a number of ways. A transgenic organism is one that has an extra or exogenous fragment of DNA incorporated into its genome, sometimes replacing an endogenous piece of DNA. In order to achieve stable inheritance of the extra or exogenous DNA, the integration event must occur in a cell type that can give rise to functional germ cells. The two animal cell types that are used for generating transgenic animals are fertilized egg cells and embryonic stem cells. Embryonic stem (ES) cells can be returned from *in vitro* culture to a "host" embryo where they become incorporated into the developing

animal and can give rise to transgenic cells in all tissues, including germ cells. The ES cells are transfected in culture and then the mutation is transmitted into the germline by injecting the cells into an embryo. The animals carrying mutated germ cells are then bred to produce transgenic offspring. The use of ES cells to make genetic changed in the mouse germline is well recognized. For a reviews of this technology, those of skill in the art are referred to Bronson & Smithies, *J. Biol. Chem.*, 269(44), 27155-27158, 1994; Torres, *Curr. Top. Dev. Biol.*, 36, 99-114; 1998 and the references contained therein.

Generally, blastocysts are isolated from pregnant mice at a given stage in development, for example, the blastocyst from mice may be isolated at day 4 of development (where day 1 is defined as the day of plug), into an appropriate buffer that will sustain the ES cells in an undifferentiated, pluripotent state. ES cell lines may be isolated by a number of methods well known to those of skill in the art. For example, the blastocysts may be allowed to attach to the culture dish and approximately 7 days later, the outgrowing inner cell mass picked, trypsinized and transferred to another culture dish in the same culture media. ES cell colonies appear 2-3 weeks later with between 5-7 individual colonies arising from each explanted inner cell mass. The ES cell lines can then be expanded for further analysis. Alternatively, ES cell lines can be isolated using the immunosurgery technique (described in Martin, *Proc. Natl. Acad. Sci. USA* 78:7634-7638, 1981) where the trophectoderm cells are destroyed using anti-mouse antibodies prior to explanting the inner cell mass.

In generating transgenic animals, the ES cell lines that have been manipulated by homologous recombination are reintroduced into the embryonic environment by blastocyst injection (as described in Williams *et al.*, *Cell* 52:121-131, 1988). Briefly, blastocysts are isolated from a pregnant mouse and expanded. The expanded blastocysts are maintained in oil-drop cultures at 4°C for 10 minutes prior to culture. The ES cells are prepared by picking individual colonies, which are then incubated in phosphate-buffered saline, 0.5 mM EGTA for 5 minutes; a single cell suspension is prepared by incubation in a trypsin-EDTA solution containing 1% (v/v) chick serum for a further 5 minutes at 4°C. Five to twenty ES cells (in Dulbecco's modified Eagle's Medium with 10% (v/v) fetal calf serum and 3,000 units/ml DNAase

1 buffered in 20 mM HEPES [pH 8]) are injected into each blastocyst. The blastocysts are then transferred into pseudo-pregnant recipients and allowed to develop normally. The transgenic mice are identified by coat markers (Hogan *et al.*, Manipulating the Mouse Embryo, Cold Spring Harbor, N.Y. (1986)). Additional methods of isolating and propagating ES cells may be found in, for example, U.S. Patent No. 5,166,065; U.S. Patent No. 5,449,620; U.S. Patent No. 5,453,357; U.S. Patent No. 5,670,372; U.S. Patent No. 5,753,506; U.S. Patent No. 5,985,659, each incorporated herein by reference.

An alternative method involving zygote injection method for making transgenic animals is described in, for example, U.S. Patent No. 4,736,866, incorporated herein by reference. Additional methods for producing transgenic animals are generally described by Wagner and Hoppe (U.S. Patent No. 4,873,191; which is incorporated herein by reference), Brinster *et al. Proc. Nat'l Acad. Sci. USA,* 82(13) 4438-4442, 1985; which is incorporated herein by reference in its entirety) and in *Manipulating the Mouse Embryo; A Laboratory Manual*, 2nd edition (eds., Hogan, Beddington, Costantimi and Long, Cold Spring Harbor Laboratory Press, 1994; which is incorporated herein by reference in its entirety).

Briefly, this method involves injecting DNA into a fertilized egg, or zygote, and then allowing the egg to develop in a pseudo-pregnant mother. The zygote can be obtained using male and female animals of the same strain or from male and female animals of different strains. The transgenic animal that is born, the founder, is bred to produce more animals with the same DNA insertion. In this method of making transgenic animals, the new DNA typically randomly integrates into the genome by a non-homologous recombination event. One to many thousands of copies of the DNA may integrate at a site in the genome

Generally, the DNA is injected into one of the pronuclei, usually the larger male pronucleus. The zygotes are then either transferred the same day, or cultured overnight to form 2-cell embryos and then transferred into the oviducts of pseudo-pregnant females. The animals born are screened for the presence of the desired integrated DNA.

DNA clones for microinjection can be prepared by any means known in the art. For example, DNA clones for microinjection can be cleaved with enzymes appropriate for removing the bacterial plasmid sequences, and the DNA fragments electrophoresed on 1% agarose gels in TBE buffer, using standard techniques. The DNA bands are visualized by staining with ethidium bromide, and the band containing the expression sequences is excised. The excised band is then placed in dialysis bags containing 0.3 M sodium acetate, pH 7.0. DNA is electroeluted into the dialysis bags, extracted with a 1:1 phenol:chloroform solution and precipitated by two volumes of ethanol. The DNA is redissolved in 1 ml of low salt buffer (0.2 M NaCl, 20 mM Tris, pH 7.4, and 1 mM EDTA) and purified on an Elutip-D™ column. The column is first primed with 3 ml of high salt buffer (1 M NaCl, 20 mM Tris, pH 7.4, and 1 mM EDTA) followed by washing with 5 ml of low salt buffer. The DNA solutions are passed through the column three times to bind DNA to the column matrix. After one wash with 3 ml of low salt buffer, the DNA is eluted with 0.4 ml high salt buffer and precipitated by two volumes of ethanol. DNA concentrations are measured by absorption at 260 nm in a UV spectrophotometer. For microinjection, DNA concentrations are adjusted to 3 mg/ml in 5 mM Tris, pH 7.4 and 0.1 mM EDTA.

Additional methods for purification of DNA for microinjection are described in Hogan *et al.* Manipulating the Mouse Embryo (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1986), in Palmiter *et al. Nature* 300:611 (1982); in The Qiagenologist, Application Protocols, 3rd edition, published by Qiagen, Inc., Chatsworth, CA.; and in Sambrook *et al. Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1989).

In an exemplary microinjection procedure, female mice six weeks of age are induced to superovulate. The superovulating females are placed with males and allowed to mate. After approximately 21 hours, the mated females are sacrificed and embryos are recovered from excised oviducts and placed in an appropriate buffer, *e.g.,* Dulbecco's phosphate buffered saline with 0.5% bovine serum albumin (BSA; Sigma). Surrounding cumulus cells are removed with hyaluronidase (1 mg/ml). Pronuclear embryos are then washed and placed in Earle's balanced salt solution containing 0.5 % BSA in a 37.5°C incubator with a humidified atmosphere at 5%

CO_2, 95% air until the time of injection. Embryos can be implanted at the two-cell stage.

Randomly cycling adult female mice are paired with vasectomized males. C57BL/6 or Swiss mice or other comparable strains can be used for this purpose. Recipient females are mated at the same time as donor females. At the time of embryo transfer, the recipient females are anesthetized with an intraperitoneal injection of 0.015 ml of 2.5 % avertin per gram of body weight. The oviducts are exposed by a single midline dorsal incision. An incision is then made through the body wall directly over the oviduct. The ovarian bursa is then torn with watchmakers forceps. Embryos to be transferred are placed in DPBS (Dulbecco's phosphate buffered saline) and in the tip of a transfer pipette (about 10 to 12 embryos). The pipette tip is inserted into the infundibulum and the embryos transferred. After the transfer, the incision is closed by two sutures. The pregnant animals then give birth to the founder animals which are used to establish the transgenic line.

I. Use of Prox-1-based Compositions for Diagnostic Purposes

The demonstration that Prox-1 is overexpressed in precancerous and colon cancer cells also indicates that detection of Prox-1 polynucleotides and polypeptides (including variants thereof) are useful for diagnostic purposes. Therefore, preferred aspects of the present invention are directed to methods of screening and diagnosing colon cancer in an individual.

In one preferred embodiment, diagnostic methods of the invention are practiced through the detection of the Prox-1 protein. In general, methods for detecting a polypeptide of the invention can comprise contacting a biological sample with a compound that binds to and forms a complex with the polypeptide for a period sufficient to form the complex, and detecting the complex, so that if a complex is detected, a polypeptide of the invention is detected. Prox-1 protein detection can be accomplished using antibodies specific for the protein in any of a number of formats commonly used by those of skill in the art for such detection.

For example, elsewhere in the present application, the production and characterization of monoclonal antibodies specific for Prox-1 is described. Such antibodies may be employed in ELISA-based techniques and Western blotting

techniques to detect the presence of Prox-1 in a biological sample from a subject being tested. Methods for setting up ELISA assays and preparing Western blots of a sample are well known to those of skill in the art. The biological sample can be any tissue or fluid in which colon cells or tissue might be present.

An anti-Prox-1 antibody or fragment thereof also is useful to monitor expression of this protein in individuals suffering from colon cancer. Typically, diagnostic assays entail detecting the formation of a complex resulting from the binding of an antibody or fragment thereof to Prox-1. For diagnostic purposes, the antibodies or antigen-binding fragments can be labeled or unlabeled. The antibodies or fragments can be directly labeled. A variety of labels can be employed, including, but not limited to, radionuclides, fluorescers, enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors and ligands (e.g., biotin, haptens). Numerous appropriate immunoassays are known to the skilled artisan (see, for example, U.S. Pat. Nos. 3,817,827; 3,850,752; 3,901,654 and 4,098,876). When unlabeled, the antibodies or fragments can be detected using suitable means, as in agglutination assays, for example. Unlabeled antibodies or fragments can also be used in combination with another (i.e., one or more) suitable reagent which can be used to detect antibody, such as a labeled antibody (e.g., a second antibody) reactive with the first antibody (e.g., anti-idiotype antibodies or other antibodies that are specific for the unlabeled immunoglobulin) or other suitable reagent (e.g., labeled protein A).

In one embodiment, the antibodies or fragments of the present invention can be utilized in enzyme immunoassays, wherein the subject antibody or fragment, or second antibodies, are conjugated to an enzyme. When a biological sample comprising a Prox-1 protein is combined with the subject antibodies, binding occurs between the antibodies and the Prox-1 protein. In one embodiment, a biological sample containing cells expressing a mammalian Prox-1 protein, or biological fluid containing secreted Prox-1 is combined with the subject antibodies, and binding occurs between the antibodies and the Prox-1 protein present in the biological sample comprising an epitope recognized by the antibody. These bound protein can be separated from unbound reagents and the presence of the antibody-enzyme conjugate specifically bound to the Prox-1 protein can be determined, for example, by contacting the sample with a substrate of the enzyme which produces a

color or other detectable change when acted on by the enzyme. In another embodiment, the subject antibodies can be unlabeled, and a second, labeled antibody can be added which recognizes the subject antibody.

Similarly, the present invention also relates to a method of detecting and/or quantitating expression of a mammalian Prox-1 protein or a portion of the Prox-1 protein by a cell, in which a composition comprising a cell or fraction thereof (e.g., a soluble fraction) is contacted with an antibody or functional fragment thereof which binds to a mammalian Prox-1 protein or a portion of the Prox-1 protein under conditions appropriate for binding of the antibody or fragment thereto, and binding is monitored. Detection of the antibody, indicative of the formation of a complex between antibody and or a portion of the protein, indicates the presence of the protein.

The method can be used to detect expression of Prox-1 from the cells of an individual (e.g., in a sample, such as a body fluid, such as blood, saliva or other suitable sample). The level of expression of in a biological sample of that individual can also be determined, for instance, by flow cytometry, and the level of expression (e.g., staining intensity) can be correlated with disease susceptibility, progression or risk.

In certain other diagnostic embodiments, the polynucleotide sequences encoding Prox-1 protein may be used for the diagnosis of conditions or diseases with which the expression of Prox-1 protein is associated. In general, methods for detecting Prox-1 mRNA can comprise contacting a biological sample with a compound that binds to and forms a complex with Prox-1 mRNA for a period sufficient to form the complex, and detecting the complex in a quantitative or semi-quantitative way. Such methods can also comprise amplification techniques involving contacting a biological sample with nucleic acid primers that anneal to Prox-1 mRNA or its complement, and amplifying annealed polynucleotides, so that if a polynucleotide is amplified, a polynucleotide of the invention is detected. The biological sample can be any tissue or fluid in which Prox-1-expressing colon cells might be present.

In the amplification procedures, polynucleotide sequences encoding Prox-1 protein may be used in hybridization or PCR assays of fluids or tissues from

biopsies to detect Prox-1 protein expression. Such methods may be qualitative or quantitative in nature and may include Southern or northern analysis, dot blot or other membrane-based technologies; PCR technologies; dip stick, pin, chip and ELISA technologies. All of these techniques are well known in the art and are the basis of many commercially available diagnostic kits.

One such procedure known in the art is quantitative real-time PCR. Real-time quantitative can be conveniently accomplished using the commercially available ABI PRISM™ 7700 Sequence Detection System, available from PE-Applied Biosystems, Foster City, CA and used according to manufacturer's instructions. PCR reagents can be obtained from PE-Applied Biosystems, Foster City, CA. Gene target quantities obtained by real time RT-PCR may be normalized using either the expression level of GAPDH, a gene whose expression is constant, or by quantifying total RNA using RiboGreen™ (Molecular Probes, Inc. Eugene, OR). GAPDH expression is quantified by real time RT-PCR, by being run simultaneously with the target, multiplexing, or separately. Total RNA is quantified using RiboGreen™ RNA quantification reagent from Molecular Probes. Methods of RNA quantification by RiboGreen™ are taught in Jones, L.J., et al, *Analytical Biochemistry*, 1998, *265*, 368-374. Controls are analyzed in parallel to verify the absence of DNA in the RNA preparation (-RT control) as well as the absence of primer dimers in control samples lacking template RNA. In addition, RT-PCR products may be analyzed by gel electrophoresis.

A reverse transcriptase PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Methods of reverse transcribing RNA into cDNA are well known and described in Sambrook et al., 1989. Alternative methods for reverse transcription utilize thermostable DNA polymerases. These methods are described in WO 90/07641, filed December 21, 1990.

Conditions for incubating a nucleic acid probe or antibody with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the nucleic acid probe or antibody used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization, amplification or immunological assay formats can readily be adapted to employ the nucleic acid probes or antibodies of the present

invention. Examples of such assays can be found in Chard, T., An Introduction to Radioimmunoassay and Related Techniques, Elsevier Science Publishers, Amsterdam, The Netherlands (1986); Bullock, G.R. et al., Techniques in Immunocytochemistry, Academic Press, Orlando, FL Vol. 1 (1982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P., Practice and Theory of immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1985). The tests of the present invention include cells, protein extracts of cells, or biological fluids such as, blood, serum, and plasma. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing protein extracts or membrane extracts of cells are well known in the art and can be readily be adapted in order to obtain a sample which is compatible with the system utilized.

In addition, such assays may be useful in evaluating the efficacy of a particular therapeutic treatment regime in animal studies, in clinical trials, or in monitoring the treatment of an individual patient. In order to provide a basis for the diagnosis of disease, a normal or standard measurement of Prox-1 mRNA or protein expression is established. This generally involves Prox-1 measurements from healthy colon tissue taken from one or more subjects, measured using the same or similar reagents used for the test subjects. The healthy subject preferably is matched for sex and age, and optionally, ethnicity. Deviation between standard and subject values correlates with the presence of precancerous or cancerous tissue.

Once disease is established, a therapeutic agent is administered; and a treatment profile is generated. Such assays may be repeated on a regular basis to evaluate whether the values in the profile progress toward or return to the normal or standard pattern. Successive treatment profiles may be used to show the efficacy of treatment over a period of several days or several months.

Methods to quantify the expression of a particular molecule include radiolabeling (Melby *et al.*, J Immunol Methods 159: 235-44, 1993) or biotinylating (Duplaa *et al.*, Anal Biochem 229-36, 1993) nucleotides, coamplification of a control nucleic acid, and standard curves onto which the experimental results are interpolated.

In addition to being used as diagnostic methods, screening methods also may be used in a prognostic manner to monitor the efficacy of treatment. The methods may be performed immediately before, during and after treatment to monitor treatment success. The methods also should be performed at intervals, preferably every three to six months, on disease free patients to insure treatment success.

In another embodiment of the present invention, kits are provided which contain the necessary reagents to carry out the assays of the present invention. Specifically, the invention provides a compartment kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising one of the probes or antibodies of the present invention; and (b) one or more other containers comprising one or more of the following: wash reagents, reagents capable of detecting presence of a bound probe or antibody.

In detail, a compartment kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers, or strips of plastic or paper. Such containers allow one to efficiently transfer reagents from one compartment to another compartment such that the biological sample and reagents are not cross-contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains, for example, the antibodies used in the assay, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and containers which contain the reagents used to detect the bound antibody or probe. Types of detection reagents include labeled nucleic acid probes, labeled secondary antibodies, or in the alternative, if the primary antibody is labeled, the enzymatic, or antibody binding reagents which are capable of reacting with the labeled antibody. One skilled in the art will readily recognize that the disclosed probes and antibodies of the present invention can be readily incorporated into one of the established kit formats which are well known in the art.

In further detail, kits for use in detecting the presence of a mammalian Prox-1 protein can include an antibody or functional fragment thereof which binds to a mammalian Prox-1 protein or portion of this protein, as well as one or more ancillary reagents suitable for detecting the presence of a complex between the

antibody or fragment and Prox-1 or portion thereof. The antibody compositions of the present invention can be provided in lyophilized form, either alone or in combination with additional antibodies specific for other epitopes. The antibodies, which can be labeled or unlabeled, can be included in the kits with adjunct ingredients. For example, the antibodies can be provided as a lyophilized mixture with the adjunct ingredients, or the adjunct ingredients can be separately provided for combination by the user. Generally these adjunct materials will be present in less than about 5% weight based on the amount of active antibody, and usually will be present in a total amount of at least about 0.001% weight based on antibody concentration. Where a second antibody capable of binding to the monoclonal antibody is employed, such antibody can be provided in the kit, for instance in a separate vial or container. The second antibody, if present, is typically labeled, and can be formulated in an analogous manner with the antibody formulations described above.

J. Examples

The present invention is illustrated in the following examples, which are intended to be illustrative and not limiting. Upon consideration of the present disclosure, one of skill in the art will appreciate that many other embodiments and variations may be made in the scope of the present invention.

Example 1 provides methods and materials for the subsequent Examples.

Example 2 provides experimental results of studies designed to assess Prox-1 expression in colorectal cancer cells.

Example 3 details expression of Prox-1 in round but not in adherent subclones of the SW480 colon adenocarcinoma cell line.

Example 4 provides experimental results of Prox-1 silencing in SW480R cells.

Example 5 describes effects of Prox-1 ablation on Notch signaling in SW480R cells.

Example 6 describes the effects of suppression of Prox-1 on the growth of SW480R cells in soft agar.

Example 7 describes the effect Prox-1 suppression on prostaglandin biosynthesis.

Example 8 describes experiments aimed as assessing the effects of altered Notch signaling.

Example 9 describes experiments aimed at assessing the effects of Prox-1 suppression on the growth of SW480R tumors in nude mice.

Example 10 describes analysis of Prox-1 in natural colorectal tumors.

Example 11 describes one method for diagnosing or screening for colorectal cancer.

Example 12 describes experiments designed to compare Prox-1 expression in normal cololnic epithelium.

Example 13 describes experiments aimed at assessing Prox-1 expression in $Apc^{min/+}$ mice.

Example 14 describes studies conducted using SW480R cell line as an in vitro model to investigate the role of Prox-1 in colorectal carcinoma.

Example 15 describes experiments to characterize the effects of Prox-1 suppression and overexpression in colorectal cancer.

Example 16 describes experiments employing dominant negative mutants of Prox-1.

EXAMPLE 1

METHODS AND MATERIALS

Methods and material used or referred to in subsequent examples are set forth directly below.

Antibodies

Monoclonal mouse anti-vimentin, ß-catenin (Transduction Laboratories), Ki-67 (Pharmingen) and chromogranin A (Ab-3, NeoMarkers), monoclonal rat anti-BrdU (Harlan Seralab) and polyclonal rabbit anti-Prox-1 were

obtained from the indicated commercial sources. The fluorochrome-conjugated secondary antibodies were obtained from Jackson Immunoresearch.

For production of Prox-1 antibodies cDNA encoding Prox-1 homeobox domain and prospero domain (amino acids 578-750 of human Prox-1, SEQ ID NO: 3) was subcloned into pGEX2t vector to produce GST-Prox-1 fusion construct. This construct was expressed in *E. coli* and the GST-Prox-1 fusion protein from *E. coli* was purified using glutathione Sepharose according to the manufacturer's instructions (Amersham, Piscataway, NJ). Fusion protein was used to immunize rabbits according to a standard protocol. Prox-1-specific antibodies were isolated from rabbit serum using sequential columns with GST- and GST-Prox-1-coupled to vinylsulfone agarose resin (Sigma). Purified antibody recognized an 85 kD protein in lysates from 293T cells transfected with Prox-1 but not from cells transfected with the empty vector.

Synthetic siRNAs

siRNA duplexes were prepared from synthetic 21 nucleotide RNAs (Dharmacon Research). siRNA sequences were: 5'-CUGCAAGCUGGAUAGUGAAGU-3' (Prox-1 siRNA A16 sense) (SEQ ID NO: 4); 5'-UUCACUAUCCAGCUUGCAGAU-3' (Prox-1 siRNA A16 antisense) (SEQ ID NO: 5); 5'-CUAUGAGCCAGUUUGAUAUUU-3' (Prox-1 siRNA A25 sense) (SEQ ID NO: 6); 5'- AUAUCAAACUGGCUCAUAGUU-3' (Prox-1 siRNA A25 antisense) (SEQ ID NO: 7).

EGFP-targeting control siRNA A18 was essentially as described (Lewis et al., 2002) except that instead of thymidine 3' overhangs uracil overhangs were used; GACGUAAACGGCCACAAGUUU (EGFP siRNA A18 sense) (SEQ ID NO: 8); ACUUGUGGCCGUUUACGUCUU (EGFP siRNA A18 antisense) (SEQ ID NO: 9).

siRNAs were 2'-ACE deprotected according to the manufacturer's instructions, dried in vacuum, resuspended in 400µl water, dried again, resuspended in water, and annealed to form duplex siRNAs. For annealing equimolar amounts of siRNA strands (approximately 50-100µM) were incubated in annealing buffer (100mM potassium acetate 30mM Hepes–KOH pH 7.4, 2mM magnesium acetate) for

5 min at +95°C followed by 30 min at +37°C and 30 min at +25°C. After annealing the siRNA concentration was measured by spectrometry and siRNA aliquoted and stored at -20°C.

Cell culture, transfection, and soft agar assay

SW480 cells were obtained from ATCC (CCL-228) and cultured in RPMI-1640 supplemented with 10% fetal bovine serum, 1 mM glutamine and antibiotics. HepG2 cells were cultured in DMEM, containing 10% fetal bovine serum 1 mM glutamine and antibiotics.

Transfection of siRNAs was carried out using Lipofectamine 2000 (Invitrogen) according to manufacturer's instructions using 0.5% (v/v) lipofectamine 2000 reagent for SW480R and 0.4% (v/v) lipofectamine 2000 for adherent SW480 cells and either 20nM or 100nM (f.c.) of siRNA. Transfections were carried out in antibiotic-free media for 4-6 hours before changing cells back to normal culture media. For long-term experiments siRNA transfections were repeated after 48-72h from previous transfection (at protein level the silencing effect was seen to remain efficient for at least 96h). Normally approximately 90-95% transfection efficiency was achieved. Opti-MEM (Invitrogen) medium was used in preparation of transfection mixtures.

For luciferase assays, cells were transfected with Green Fluorescent Protein small interfering RNA (GFPsi RNA) or Prox-1 siRNAs 72 h prior to the transfection with the firefly lucefarese reporter constructs CBF1-luc, control pGL2-luc (Promega), TOPFlash and FOPFlash (Upstate). To normalize the transfection efficiency, cells were co-transfected with the Renilly firefly reporter pRL-TK (Promega). 36 h after the last transfection cells were lysed and lysates were analyzed for the luciferase activity using Dual-Luciferase™ kit according to the manufacturer's instructions (Promega).

For soft agar assay, $2x10^3$ and $2x10^4$ cells were seeded in triplicate in 1 ml of 0.33% (w/v) agar (Difco) containing D-MEM, 10% fetal bovine serum, 1 mM glutamine and antibiotics in 6-well plates containing 1ml of 0.5% bottom agar layer. Cells were fed twice a week, and number of colonies per plate was scored after two weeks in culture.

RNA isolation, Northern, and Western blotting

Total RNA was isolated and DNAseI treated in RNeasy columns (Qiagen). For Cancer Array analysis, filters were hybridized in ExpressHyb with 32P-labeled probes for LYVE-1 and Prox-1 according to the manufacturer's instructions (Clontech). For Northern analysis, the blots were hybridized in Ultrahyb solution (Ambion) with 32P-labeled probes produced by RT-PCR using RNA from SW480R or SW480A cells. The primers were designed to amplify 300-700 bp of the coding sequence, and all PCR-fragments were sequenced to confirm their identity.

For the Affymetrix® gene expression analysis, sample preparations and hybridizations were carried out as described (Petrova et al. *Embo J* 21: 4593-9, 2002), using RNA extracted from two clones of SW480R or SW480A cells, or from two independent transfections of two different clones of SW480R cells with GFP siRNA or Prox-1 siRNA A16. To confirm the latter results, another transfection was carried out using Prox siRNA A25. To exclude the non-specific effects due to the transfection itself, non-transfected SW480R cells grown in parallel were also analyzed.

For Western blotting $2x10^5$ cells were lysed in 500 µl of sample buffer, lysates were separated using 10% PAGE and transferred to the nitrocellulose membranes (Schleisher&Schull) using semi-dry transfer method for 1 h at 300 mA. Membranes were blocked in 5% non-fat dry milk, 0.1% Tween-20 in 50 mM Tris-HCl, pH 7.4, 150 mM NaCl, and incubated overnight with primary antibodies. Bound primary antibodies were detected using HRP-conjugated corresponding secondary antibodies and the ECL detection method (KPL).

Immunofluorescence and immunohistochemistry

The cells were cultured on coverslips, fixed with MetOH and stained with the primary antibodies and fluorochrome-conjugated secondary antibody. F-actin was stained using TexasRed-conjugated phalloidin (Molecular Probes). Cells were counterstained with Hoechst 33258 fluorochrome (Sigma) and viewed in Zeiss Axioplan 2 fluorescent microscope.

For tissue staining staining, colon tumors and normal colon samples were embedded in Tissue-Tek® (Sakura), frozen and sectioned. The 4µm sections

were fixed in cold methanol for 10 min and stained with the primary antibodies followed by peroxidase staining using Vectastain Elite ABC kit (Vector Laboratories) and 3-amino-9-ethyl carbazole (Sigma), or by detection using fluorchrome conjugated secondary antibodies.

EXAMPLE 2

Prox-1 mRNA is Elevated in Colorectal Tumors

Experiments were conducted to assess the expression of Prox-1 mRNA in human cancers using a cancer gene profiling array filter, which contains cDNAs from about 250 human cancers and corresponding normal control tissues. Prox-1 mRNA was significantly increased in 35 out of 53 samples of colorectal cancers. In contrast, only rarely or not at all was any increase seen in samples from breast, uterine, lung, kidney, ovarian, or thyroid tumors (Fig. 1A, B, and C). Probes for Prox-1 (Fig. 1A) and the lymphatic endothelial marker LYVE-1 (Fig. 1B) were used. Fig. 1C demonstrates quantification of dot blot in Fig. 1A, the asterisk indicating tumor samples in which Prox-1 expression is significantly different from that of the normal tissue ($P<0.005$). Expression of Prox-1 was low or absent in all kidney cancer samples studied. Prox-1 is a marker for lymphatic vessels, which are abundant both in normal colonic submucosa and around colon carcinomas (White et al., *Cancer Res.* 62: 1669-75 (2002)). Therefore, the filter to the probe for the lymphatic endothelial hyaluronan receptor LYVE-1 was hybridized. Unlike Prox-1, LYVE-1 levels were higher in the normal samples, suggesting that the increased expression cannot be attributed to the lymphatic vessels (Fig. 1B).

Experiments were further conducted to assess the expression of Prox-1 in colon cancers and premalignant colonic lesions using affinity purified antibodies raised against Prox-1 homeobox and prospero domains, which are conserved between the mouse and human proteins. Staining of a panel of mouse tissues and E12.5 and E17.5 embryos revealed specific nuclear staining for Prox-1 in the previously reported sites of expression such as in lymphatic vessels, lens fiber cells and in a subset of neurons in the neural tube. Staining of eleven human colorectal adenomas and nine carcinomas and adjacent normal mucosa revealed increased expression of Prox-1 in nine adenomas and in six carcinomas (Fig. 2A-I). Increased Prox-1 staining was observed in all cells in seven adenomas and in two carcinomas, whereas in the other

lesions a heterogeneous expression of Prox-1 occurred. In one tumor sample, no specific staining for Prox-1 was seen, while strong expression was observed in intratumoral lymphatic vessels.

Double immunofluorescent staining for Prox-1 and the neuroendocrine marker chromogranin A or proliferation marker Ki-67 was conducted in normal colonic epithelial cells. Nuclei were visualized with Hoechst 333421. In the normal colonic mucosa, Prox-1 was strongly expressed in some epithelial cells, a subset of which was positive for the pan-neuroendocrine marker chromogranin A. In addition, a weaker but significant Prox-1 expression was observed in the bottom of the crypts below the cell proliferation zone identified by staining for the Ki-67 antigen. The location of Prox-1 positive cells at the base of the crypts corresponds to the position of the intestinal stem cells (Bach et al., *Carcinogenesis* 21: 469-76 (2000)).

EXAMPLE 3

PROX-1 IS EXPRESSED IN ROUND BUT NOT IN ADHERENT SUBCLONES OF THE SW480 COLON ADENOCARCINOMA CELL LINE.

Additional studies were conducted to compare Prox-1 expression in various cells. No Prox-1 expression was seen in the majority of tumor cell lines studied. However, Prox-1 was mRNA was present in hepatocellular carcinoma cell line HepG2 and the colon carcinoma cell line SW480. BEC, blood endothelial cells, CAEC, coronary artery endothelial cells, and LEC, lymphatic endothelial cells, served as negative and positive controls. Immunofluorescent staining of Prox-1 revealed strong expression in all HepG2 cells, whereas only a subset of SW480 cells were Prox-1 positiveDouble immunofluorescent staining for Prox-1 and for ß-catenin or for the F-actin marker phalloidin demonstrated that Prox-1 expression is restricted to weakly adherent round SW480 cells which did not display focal adhesions or actin stress fibers, and that Prox-1 was very weakly expressed the adherent cells. The existence of two subtypes of cells in the SW480 cultures has been reported previously (Palmer, H. G. et al., *J Cell Biol.* 154: 369-87, 2001; Tomita, N. et al., Cancer Res. 52; 6840-7, 1992). The SW480R (round) cells displayed anchorage independent growth *in vitro* and highly malignant phenotype *in vivo*, whereas the SW480A (adherent) cells did not grow well in soft agar and formed small and well differentiated tumors when implanted into nude mice.

Several SW480R and SW480A clones were isolated, which could be continuously grown for at least 20 passages without conversion of phenotypes. SW480R and SW480A cells differed by the levels of Prox-1, as determined by Northern and Western blotting, with much higher expression in the round cells, and weak, if any, expression in the Adherent ones. The gene expression profiles of SW480R and SW480A cells were compared using oligonucleotide microarrays containing 22,000 annotated human genes, and identified about 1,000 genes whose expression differed by more than fourfold between these two cell types (Table I). SW480 cells were stained for intermediate filament protein vimentin and Prox-1. Northern blotting and hybridization were used for transcripts. Hybridization for GAPDH was used as a control. A striking difference was observed in the expression of cytoskeletal and cell adhesion proteins. In agreement with their decreased adhesion and round cell shape, the SW480R cells lacked many components of the actin, intermediate filament and microtubule networks, such as gelsolin, filamins A and B, ezrin, moesin, vimentin, various integrins, and tubulins (Table I). These cells expressed higher levels of the protoncogene c-met, as well as the receptor tyrosine kinase FGFR-4, which has been associated with malignant transformation in colorectal and other cancer (Bange, J. et al., *Cancer Res.* 62: 840-7, 2002; Cavallaro, U., Niedermeyer, J., Fuxa, M. & Christofori, G., *Nat. Cell Biol.* 3: 650-7, 2001; Yamada, S. M. et al., *Neurol Res.* 24: 244-8, 2002), and low levels of the tumor suppressor p21Cip1. FGFR-4 is a target for therapeutic intervention according to the invention, alone or in combination with Prox-1. Intervention using the same classes of inhibitors as described for Prox-1, as well as antibodies and antibody fragment substances, is specifically contemplated. In addition, all three tissue inhibitors of matrix metalloproteinases were absent from the SW480R cells, which may further account for their increased tumor growth *in vivo*. In contrast, the SW480A cells expressed higher levels of the chemokine receptor CXCR4, which is expressed in the normal colonic epithelium (Jordan et al., *J Clin Invest* 104, 1061-9, 1999). In summary, the gene expression profile of the SW480R cells correlates well with a highly aggressive transformed phenotype, whereas the SW480A cells display more differentiated features typical of cells in the colonic crypts.

Table I. Examples of groups of genes differentially expressed in round versus adherent SW480 clones. Two round and two adherent clones were analyzed.

Gene function and name	UniGene cluster	Gene symbol	Log_2 ratio, average	St. dev
1. Cytoskeleton and adhesion				
collagen, type XIII, alpha 1	Hs.211933	COL13A1	-5.6	0.9
fibronectin 1	Hs.287820	FN1	-5.2	0.5
integrin, alpha 7	Hs.74369	ITGA7	-4.3	0.3
vimentin	Hs.297753	VIM	-4.1	0.6
filamin B, beta (actin binding protein 278)	Hs.81008	FLNB	-3.8	0.7
integrin, beta 5	Hs.149846	ITGB5	-3.6	0.5
tubulin, beta polypeptide	Hs.274398	TUBB	-3.3	0.7
PTPL1-associated RhoGAP 1	Hs.70983	PARG1	-3.0	0.5
collagen, type IX, alpha 3	Hs.53563	COL9A3	-2.8	0.8
paralemmin	Hs.78482	PALM	-2.7	0.2
PDZ and LIM domain 1 (elfin)	Hs.75807	PDLIM1	-2.7	0.2
cadherin 11, type 2, OB-cadherin (osteoblast)	Hs.75929	CDH11	-2.6	0.7
myosin IC	Hs.286226	MYO1C	-2.6	0.6
integrin, alpha 3	Hs.265829	ITGA3	-2.6	0.4
discs, large (Drosophila) homolog 1	Hs.154294	DLG1	-2.5	0.1
integrin, alphaV	Hs.295726	ITGAV	-2.5	0.3
CDC42 effector protein (Rho GTPase binding) 3	Hs.260024	CDC42EP3	-2.4	0.4
ephrin-B1	Hs.144700	EFNB1	-2.3	0.4
FERM, RhoGEF (ARHGEF) and pleckstrin domain protein 1	Hs.183738	FARP1	-2.3	0.4
myosin ID	Hs.39871	MYO1D	-2.1	0.2
PDZ and LIM domain 2 (mystique)	Hs.379109	PDLIM2	-2.1	0.4
tubulin beta-5	Hs.274398	TUBB-5	-1.9	0.3
erythrocyte membrane protein band 4.1-like 1	Hs.26395	EPB41L1	-1.9	0.1
gelsolin (amyloidosis, Finnish type)	Hs.290070	GSN	-1.9	0.3
laminin, gamma 1 (formerly LAMB2)	Hs.432855	LAMC1	-1.8	0.1
ras homolog gene family, member E	Hs.6838	ARHE	-1.7	0.2
IQ motif containing GTPase activating protein 1	Hs.1742	IQGAP1	-1.7	0.3
tight junction protein 1 (zona occludens 1)	Hs.74614	TJP1	-1.7	0.4
catenin (cadherin-associated protein), alpha-like 1	Hs.58488	CTNNAL1	-1.7	0.6
collagen, type XVIII, alpha 1	Hs.78409	COL18A1	-1.6	0.1
filamin A, alpha (actin binding protein 280)	Hs.195464	FLNA	-1.6	0.2
actin related protein 2/3 complex, subunit 1A, 41kDa	Hs.90370	ARPC1A	-1.5	0.3
alpha integrin binding protein 63	-	AIBP63	-1.4	0.3
spectrin, alpha, non-erythrocytic 1 (alpha-fodrin)	Hs.77196	SPTAN1	-1.4	0.2
villin 2 (ezrin)	Hs.155191	VIL2	-1.4	0.3
actin related protein 2/3 complex, subunit 1B, 41kDa	Hs.433506	ARPC1B	-1.3	0.1
plakophilin 4	Hs.152151	PKP4	-1.3	0.3
ras homolog gene family, member C	Hs.179735	ARHC	-1.1	0.1
moesin	Hs.170328	MSN	-1.1	0.1

myristoylated alanine-rich protein kinase C substrate	Hs.75607	MARCKS	-1.1	0.2
2. Tumor growth and invasion				
tissue inhibitor of metalloproteinase 2	Hs.6441	TIMP2	-2.3	0.21
tissue inhibitor of metalloproteinase 3	Hs.245188	TIMP3	-1.5	0.14
Cyclin-dependent kinase inhibitor 1A (p21, Cip1)	Hs.179665	CDKN1A	-2.5	0
tissue inhibitor of metalloproteinase 1	Hs.5831	TIMP1	-1.5	0.4
met proto-oncogene (hepatocyte growth factor receptor)	Hs.316752	MET	2.6	0.46
Fibroblast growth receptor 4	Hs.165950	FGFR4	3.9	0.76
3. Expressed in normal intestinal epithelium				
CXCR4	Hs.89414	CXCR4	-1.3	0.1
solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	Hs.22891	SLC7A8	-1.8	
4. Notch pathway				
Notch homolog 2 (Drosophila)	Hs.8121	NOTCH2	-1.4	0.15
hairy homolog (Drosophila), HES1	Hs.250666	HRY	-2.1	0.2
jagged 2	Hs.166154	JAG2	1.6	0.61
5. Wnt pathway				
wingless-type MMTV integration site family, member 5A	Hs.152213	WNT5A	-5.8	0.12
dickkopf homolog 3	Hs.4909	DKK3	-5.6	1.21
wingless-type MMTV integration site family, member 6	Hs.29764	WNT6	-4.2	0.23
frizzled homolog 7 (Drosophila)	Hs.173859	FZD7	-4.1	0.65
frizzled homolog 2 (Drosophila)	Hs.81217	FZD2	-3.7	0.56
frizzled homolog 10 (Drosophila)	Hs.31664	FZD10	2.97	0.86
dickkopf homolog 4	Hs.159311	DKK4	7.37	0.71

EXAMPLE 4

PROX-1 SILENCING IN SW480R CELLS LEADS TO A DIFFERENTIATED AND QUIESCENT PHENOTYPE.

Experiments were conducted to investigate whether Prox-1 plays role in the generation and maintenance of the highly transformed phenotype. Prox-1 mRNA and protein in the SW480R cells was suppressed using Prox-1 targeting siRNA. Absence of Prox-1 in Prox-1 siRNA but not the control GFP siRNA transfected cells was confirmed by immunofluorescent staining, and nuclei were visualized with Hoechst 33342. Prox-1 siRNA-transfected cells but not the untransfected or GFP siRNA transfected cells underwent a morphological change, which became visible by 72 hours and persisted at least for 10 days after the transient transfection. The Prox-1 siRNA transfected cells become first more elongated and

displayed extensive membrane ruffling. Eventually the Prox-1 siRNA cells started to spread on the plate and a number of increased actin stress fibers could be visualized by phalloidine staining. BrdU incorporation experiments demonstrated that the Prox-1 siRNA transfected cells proliferated at the lower rate than GFPsi or nontransfected cells (22±0.5% of BrdU positive cells in Prox-1 siRNA A16, 18±1% Prox-1 siRNA A25 vs 34±4% GFP siRNA).

Changes in the gene expression profiles of the SW480R and SW480A cells 120 and 240 h posttransfection, when the morphological changes were apparent, were also analyzed. Only 29 down-regulated and 120 upregulated genes in Prox-1 siRNA versus GFP siRNA transfected cells (Table II) were identified. 41% of these genes were differentially expressed between the SW480R and SW480A cells, suggesting that Prox-1 at least partially determines the phenotype of SW480R cells. The ablation of Prox-1 led to upregulation of a number of known epithelial markers, such as annexin A1, CRPB2, S100A3, and EMP1, along with the increase in cell adhesion molecules OB-cadherin and integrins beta7, beta5 and alpha 1. In line with the observed growth arrest, also observed was the decrease in c-myc and a strong increase of CDK inhibitor p21Cip1. Highly similar changes in gene expression profile were observed when another unrelated Prox-1si RNA was used, suggesting that the cellular effects are due to the specific targeting of Prox-1, and they did not result from off-target silencing. In addition, titration experiments demonstrated that the induction of p21 and other target genes occurred even at the low (20 nM) concentration of Prox-1 siRNAs but not of the control GFP siRNA. Also, the mentioned gene changes were not observed in Prox-1 negative SW480A cells transfected with siRNAs at 100 nm concentration. The transfection efficiency was controlled using another siRNA, which successfully suppressed the expression of the target gene in SW480A cells.

Table II. Genes regulated by Prox-1 in SW480R cells. Asterisk indicates genes that were flagged as absent in either Prox-1 siRNA or GFP siRNA treated cells. Genes differentially expressed between SW480R and SW480ADH cells are shown in bold.

Genes down-regulated in the absence of Prox-1	UniGene cluster	Gene symbol	Log_2 ratio, average	stdev
Nebulette	Hs.5025	NEBL	-2.0	0.4
transforming growth factor, beta-induced, 68kDa	Hs.118787	**TGFBI**	**-1.9**	**0.1**
trinucleotide repeat containing 9	Hs.110826	**TNRC9**	**-1.9**	**0.2**
insulin-like growth factor binding protein 3	Hs.77326	IGFBP3	-1.6	0.0
calpain 1, (mu/I) large subunit	Hs.2575	CAPN1	-1.5	0.3
inhibitor of DNA binding 1	Hs.75424	**ID1**	**-1.5**	**0.3**
midkine (neurite growth-promoting factor 2)	Hs.82045	MDK	-1.5	0.1
FK506 binding protein 11, 19 kDa	Hs.24048	FKBP11	-1.4	0.1
caspase recruitment domain family, member 10	Hs.57973	CARD10	**-1.3**	0.1
inhibin, beta B (activin AB beta polypeptide)	Hs.1735	**INHBB**	**-1.3**	**0.2**
L1 cell adhesion molecule	Hs.1757	L1CAM	-1.2	0.1
glutathione peroxidase 2 (gastrointestinal)	Hs.2704	**GPX2**	**-1.2**	**0.0**
eukaryotic translation elongation factor 1 alpha 2	Hs.2642	**EEF1A2**	**-1.2**	**0.2**
hypothetical protein FLJ11149	Hs.37558	FLJ11149	-1.2	0.2
potassium voltage-gated channel, subfamily H (eag-related), member 2	Hs.188021	KCNH2	**-1.1**	0.1
KIAA0182 protein	Hs.75909	**KIAA0182**	**-1.1**	**0.0**
lectin, galactoside-binding, soluble, 1 (galectin 1)	Hs.382367	LGALS1	-1.1	0.1
Homo sapiens cDNA FLJ41000 fis,	-	-	-1.1	0.3
ephrin-B2	Hs.30942	**EFNB2**	**-1.1**	**0.1**
v-myc myelocytomatosis viral oncogene homolog (avian)	Hs.79070	**MYC**	**-1.1**	0.1
S100 calcium binding protein A14	Hs.288998	S100A14	-1.1	0.2
Alpha one globin [Homo sapiens], mRNA sequence*			**-1.1**	**0.1**
hypothetical protein FLJ10986*	Hs.273333	**FLJ10986**	**-1.0**	**0.0**
hypothetical protein FLJ11149	Hs.37558	**FLJ11149**	**-1**	**0.0**
myelin transcription factor 1*		**MYT1**	**-1.0**	**0.0**
nucleolar autoantigen (55kD) similar to rat synaptonemal complex protein*	Hs.446459	SC65	***-1.0***	0.1
tumor necrosis factor receptor superfamily, member 6b, decoy	Hs.455817	TNFRSF6B	**-1.0**	0.1
jagged 2	Hs.166154	**JAG2**	**-1.0**	**0.1**
mitochondrial ribosomal protein S2	Hs.20776	MRPS2	-1.0	0.1
Total: 29 genes				

Genes up-regulated in the absence of Prox1	UniGene cluster	Gene symbol	Log2 ratio. average	Stdev
insulin-like growth factor binding protein 7*	**Hs.119206**	**IGFBP7**	**5.8**	**0.4**
chitinase 3-like 1 (cartilage glycoprotein-39)*	Hs.75184	CHI3L1	5.3	0.8
chemokine (C-X-C motif) receptor 4*	**Hs.89414**	**CXCR4**	**4.5**	**1.1**
semaphorin 3C*	Hs.171921	SEMA3C	4.5	4.5
cadherin 11, type 2, OB-cadherin (osteoblast)*	Hs.75929	**CDH11**	**3.8**	**0.3**
annexin A1	**Hs.78225**	ANXA1	3.7	1.1
hypothetical protein MGC10796*	-	**MGC1079 6**	**3.3**	**0.4**
CD44 antigen	Hs.169610	**CD44**	**2.6**	**1.1**
Homo sapiens clone 23785 mRNA sequence	-	-	**2.9**	0.4
epithelial membrane protein 1*	**Hs.79368**	**EMP1**	**2.9**	**0.1**
inhibitor of DNA binding 2, dominant negative helix-loop-helix protein*	**Hs.180919**	**ID2**	**2.8**	**0.1**
Human HepG2 3' region cDNA, clone hmd1f06, mRNA sequence	-	-	**2.8**	**0.3**
tumor necrosis factor receptor superfamily, member *11b (osteoprotegerin)	**Hs.81791**	**TNFRSF1 1B**	**2.6**	**0.7**
likely homolog of mouse glucuronyl C5-epimerase*	Hs.183006	GLCE	2.6	1.1
ribonuclease, RNase A family, 1 (pancreatic)*	Hs.78224	RNASE1	2.6	0.1
apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B*	**Hs.226307**	**APOBEC 3B**	**2.5**	**0.1**
hydroxyprostaglandin dehydrogenase 15-(NAD)*	**Hs.77348**	**HPGD**	**2.5**	**1.1**
NPD009 protein	Hs.283675	NPD009	2.5	0.6
integrin, beta 7*	Hs.1741	ITGB7	2.4	0.1
fibroblast growth factor 20*	Hs.154302	FGF20	2.3	1.0
KIAA0455 gene product	Hs.13245	KIAA0455	2.3	1.3
CAMP-specific phosphodiesterase 8B1 [Homo sapiens], mRNA sequence*	Hs.78106	PDE8B	2.3	0.4
ectodermal-neural cortex (with BTB-like domain)*	**Hs.104925**	**ENC1**	**2.3**	**0.2**
frizzled homolog 1 (Drosophila)*	Hs.94234	FZD1	2.3	0.8
S100 calcium binding protein A3*	Hs.433168	S100A3	2.2	0.6
zeta-chain (TCR) associated protein kinase 70kDa*	Hs.234569	ZAP70	2.2	1.1
platelet derived growth factor C*	Hs.43080	PDGFC	2.1	0.1
cystatin D *	Hs.121489	CST5	2.1	0.3
CCAAT/enhancer binding protein (C/EBP), delta	**Hs.76722**	**CEBPD**	**2.1**	**0.1**
sorbin and SH3 domain containing 1	Hs.108924	**SORBS1**	**2.1**	**0.5**
metallothionein 2A	Hs.118786	MT2A	2.0	0.6
RAS guanyl releasing protein 1 (calcium and DAG-regulated)	Hs.182591	RASGRP1	2.0	0.4
checkpoint suppressor 1	**Hs.211773**	**CHES1**	**2.0**	**0.4**
chondroitin beta1,4 N-acetylgalactosaminyltransferase*	**Hs.11260**	**ChGn**	**2.0**	**0.4**
filamin B, beta (actin binding protein 278)*	**Hs.81008**	**FLNB**	**2.0**	**0.4**
aldehyde dehydrogenase 1 family, member A2*	Hs.95197	ALDH1A2	2.0	0.6
jagged 1 (Alagille syndrome)	Hs.91143	JAG1	2.0	0.1
A kinase (PRKA) anchor protein (gravin) 12*	**Hs.788**	**AKAP12**	**1.9**	**0.1**
metallothionein 1X*	Hs.380778	MT1X	1.9	0.8
creatine kinase, mitochondrial 2 (sarcomeric)	**Hs.80691**	**CKMT2**	**1.8**	**0.6**

serum-inducible kinase	Hs.3838	SNK	1.8	0.1
CGI-130 protein	**Hs.32826**	**CGI-130**	**1.8**	**0.1**
guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1	Hs.203862	GNAI1	1.8	0.4
related to the N terminus of tre*	Hs.278526	RNTRE	1.7	0.4
solute carrier family 12 (sodium/potassium/chloride transporters), member 2	Hs.110736	SLC12A2	1.7	0.3
Human clone 23612 mRNA sequence	-	-	1.7	1.0
ankyrin repeat and SOCS box-containing 4	Hs.248062	ASB4	1.7	0.8
apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3C	Hs.8583	APOBEC3C	1.7	0.1
cellular retinoic acid binding protein 2*	**Hs.183650**	**CRABP2**	**1.7**	**0.1**
KIAA0657 protein*	**Hs.6654**	**KIAA0657**	**1.7**	**1.1**
phosphodiesterase 4D, cAMP-specific (phosphodiesterase E3 dunce homolog, Drosophila)	Hs.172081	PDE4D	1.7	0.1
autism susceptibility candidate 2	Hs.32168	AUTS2	1.6	0.4
hairy/enhancer-of-split related with YRPW motif 2*	Hs.144287	HEY2	1.6	0.0
immediate early response 5	**Hs.15725**	**IER5**	**1.6**	**0.1**
E3 ubiquitin ligase SMURF2	Hs.194477	SMURF2	1.6	0.4
ADP-ribosylation factor-like 7*	**Hs.111554**	**ARL7**	**1.6**	**1.0**
Ras and Rab interactor 2*	**Hs.62349**	**RIN2**	**1.6**	**0.4**
GS3955 protein, Tribbles homolog 2	Hs.155418	TRB2	1.6	0.5
metallothionein 1L	Hs.448357	MT1L	1.5	0.6
glutamate receptor, metabotropic 8	Hs.86204	GRM8	1.5	0.2
klotho	Hs.94592	KL	1.5	0.1
calmodulin-like 3	Hs.239600	CALML3	1.4	0.6
integrin, alpha 1	Hs.116774	ITGA1	1.4	0.1
lymphoid enhancer-binding factor 1	**Hs.44865**	**LEF1**	**1.4**	**0.4**
epithelial V-like antigen 1	Hs.116651	EVA1	1.4	0.1
likely ortholog of mouse limb-bud and heart gene*	**Hs.57209**	**LBH**	**1.4**	**0.1**
insulin induced protein 2	Hs.7089	ISG2	1.4	0.2
patched homolog (Drosophila)	Hs.159526	PTCH	1.4	0.1
chemokine-like factor super family 6	**Hs.380627**	**CKLFSF6**	**1.3**	**0.3**
lipoma HMGIC fusion partner	Hs.93765	LHFP	1.3	0.4
transforming growth factor, alpha	Hs.170009	TGFA	1.3	0.4
Homo sapiens mRNA; cDNA DKFZp762M127 (from clone DKFZp762M127), mRNA sequence	-	-	1.3	0.6
cyclin I	Hs.79933	CCNI	1.3	0.1
hyaluronan synthase 2	**Hs.159226**	**HAS2**	**1.3**	**0.5**
IQ motif containing GTPase activating protein 1	**Hs.1742**	**IQGAP1**	**1.3**	**0.5**
zinc finger protein 216	Hs.406096	ZNF216	1.3	0.2
cDNA DKFZp564O0122	-	-	1.3	0.2
aryl hydrocarbon receptor	Hs.170087	AHR	1.2	0.6
neuroepithelial cell transforming gene 1	Hs.25155	NET1	1.2	0.1
sterol-C4-methyl oxidase-like	Hs.239926	SC4MOL	1.2	0.1
tubulin, alpha 3	Hs.433394	TUBA3	1.2	0.1
BCG-induced gene in monocytes, clone 103	Hs.284205	BIGM103	1.2	0.0
cathepsin B	Hs.297939	CTSB	1.2	0.0
keratin 6A	Hs.367762	KRT6A	1.2	0.4

paraoxonase 2	Hs.169857	PON2	1.2	0.4
suppressor of cytokine signaling 5	Hs.169836	SOCS5	1.2	0.4
KIAA0877 protein	Hs.11217	KIAA0877	1.2	0.2
propionyl Coenzyme A carboxylase alpha	**Hs.80741**	**PCCA**	**1.2**	**0.2**
solute carrier family 2	**Hs.7594**	**SLC2A3**	**1.2**	**0.1**
solute carrier family 7	**Hs.22891**	**SLC7A8**	**1.2**	**0.1**
Homo sapiens mRNA; cDNA DKFZp762M127	-	-	1.2	0.1
aryl hydrocarbon receptor nuclear translocator-like	Hs.74515	ARNTL	1.1	0.3
DnaJ (Hsp40) homolog, subfamily B, member 6	Hs.181195	DNAJB6	1.1	0.3
hypothetical protein FLJ21276	-	FLJ21276	1.1	0.1
integrin, beta 5	**Hs.149846**	**ITGB5**	**1.1**	**0.1**
PTK7 protein tyrosine kinase 7	Hs.90572	PTK7	1.1	0.3
transforming growth factor, beta receptor II	Hs.82028	TGFBR2	1.1	0.1
Homo sapiens cDNA FLJ25134 fis	Hs.301306		1.1	0.0
DKFZP564A2416 protein	**Hs.5297**	**DKFZP564A2416**	**1.1**	**0.1**
dual specificity phosphatase 6	**Hs.180383**	**DUSP6**	**1.1**	**0.4**
midline 1 (Opitz/BBB syndrome)	Hs.27695	MID1	1.1	0.1
membrane protein, palmitoylated 1, 55kDa	Hs.1861	MPP1	1.1	0.1
LIM domain protein	**Hs.424312**	**RIL**	**1.1**	**0.1**
SH3-domain binding protein 5 (BTK-associated)	**Hs.109150**	**SH3BP5**	**1.1**	**0.1**
SIPL protein	Hs.64322	SIPL	1.1	0.1
tumor protein D52-like 1	**Hs.16611**	**TPD52L1**	**1.1**	**0.4**
3-hydroxy-3-methylglutaryl-Coenzyme A reductase	Hs.11899	HMGCR	1.0	0.1
homeo box B7	**Hs.819**	**HOXB7**	**1.0**	**0.1**
HIV-1 Tat interactive protein 2, 30kDa	Hs.90753	HTATIP2	1.0	0.1
insulin receptor substrate 2	**Hs.143648**	**IRS2**	**1.0**	**0.1**
tubulin beta-5	**Hs.274398**	**TUBB-5**	**1.0**	**0.0**
apoptosis antagonizing transcription factor	Hs.16178	AATF	1.0	0.1
E2F transcription factor 3	Hs.1189	E2F3	1.0	0.1
hypothetical protein FLJ12542	Hs.236940	FLJ12542	1.0	0.1
phafin 2, Pleckstrin homology domain containing, family F member 2	Hs.29724	PLEKHF2	1.0	0.1
proline 4-hydroxylase	**Hs.3622**	**P4HA2**	**1.0**	**0.1**
Homo sapiens G21VN02 mRNA, mRNA sequence, solute carrier family 5 (inositol transporters), member 3	**Hs.324787**	**SLC5A3**	**1.0**	**0.1**

EXAMPLE 5

ABLATION OF PROX-1 LEADS TO DIFFERENTIATION THROUGH UP-REGULATION OF NOTCH SIGNALING IN THE SW480R CELLS.

Activation of ß-catenin/TCF pathway plays a central role in colon tumorigenesis (Giles, R. H., van Es, J. H. & Clevers, H., *Biochim Biophys Acta* 1653: 1-24, 2003). Of interest for this study, suppression of ß-catenin/TCF signaling in

colon cancer cells decreases the levels of c-myc, increases p21Cip1 levels and induces cell cycle arrest (van de Wetering et al., *Cell* 111:, 241-50, 2002). However, suppression of Prox-1 did not affect the activity of β-catenin/TCF-responsive reporter or nuclear localization of β-catenin. Moreover, an increased expression of several β-catenin/TCF-4 target genes, such as CD44, ENC1 and Id2 was observed in the absence of Prox-1 (Table II and not shown). These data suggest that Prox-1 may act via an alternative pathway to promote growth of colon cancer cells, and that both ß-catenin/TCF activation and overexpression of Prox-1 are necessary for cell transformation. Accordingly, contemplated herein are methods of alleviating colorectal cancer whereby a Prox-1 suppressor is administered in combination with a ß-catenin/TCF signaling inhibitor. ß-catenin/TCF signaling inhibitors may include dominant negative forms of TCF-4, siRNAs and microRNAs targeting TCF-4, ß-catenin, and c-myc, as well as small molecules that would interfere with binding of ß-catenin to TCF-4 or TCF-4 to target DNA sequences. Protocols for making these types of inhibitors are detailed above with respect to Prox-1 inhibition.

The DNA and protein sequences for ß-catenin (SEQ ID NOs: 10 and 11, respectively) are published and disclosed as Genbank Accession Number NM_001904. The DNA and protein sequences for TCF-4 (SEQ ID NOs: 12 and 13, respectively) are published and disclosed as Genbank Accession Number NM_003199. Related to the ß-catenin/TCF signaling pathway is the APC gene, the sequence of which is publicly available as Genbank Accession Number NM_000038. The DNA and amino acid sequences for APC are also provided herein as SEQ ID NOs: 42 and 43, respectively. The DNA and protein sequences for C-myc (SEQ ID NOs: 44 and 45, respectively) are published and disclosed as Genbank Accession Number NM_002467.

Notch signaling has been shown to be essential for the generation of cell lineages in the crypts of the mouse small intestine. High levels of Notch are thought to suppress the expression of the basic helix-loop-helix transcription factor Math1 via the induction of the transcriptional repressor Hes1, which will lead to the differentiation of progenitor cells into enterocytes. Conversely, high levels of Math1 result in the differentiation towards the neuroendocrine, Goblet and Paneth cell types in the small intestine (Jensen, J. et al., *Nat Genet* 24: 36-44, 2000; Yang, Q.,

Bermingham, N. A., Finegold, M. J. & Zoghbi, H. Y., *Science* 294: 2155-8, 2001). Among Notch signaling components, Notch2 and its target transcription factor Hes1 levels are higher in SW480A cells in comparison with the SW480R cells, suggesting that this pathway is functionally active in these cells. Interestingly, SW480R cells express higher levels of Notch ligand Jagged2. Suppression of Prox-1 resulted in up-regulation of the Notch ligand Jagged1 and the direct target of the Notch pathway, the transcription factor Hey2, whereas the expression of Jagged2 and prostaglandin D2 synthase, previously shown to be negatively regulated by Notch signaling was suppressed (Fujimori, K. et al., *J Biol Chem* 278: 6018-26, 2003). SW480R cells were transfected with GFP siRNA or Prox-1 siRNA and GFB1-luc, TOPFlash or control FOP flash reporters. Firefly luciferase activity was normalized to Renilla luciferase activity. Up-regulation of Notch-responsive reporter GBF1-luc was observed in SW480R cells transfected with Prox-1 siRNAs. Accordingly, contemplated herein is a method of alleviating the symptoms of colorectal cancer comprising the administration of a Prox-1 suppressor in combination with a Notch agonist or target transcription factor. Notch agonists include Jagged1, Jagged2, Delta1, Delta3, Delta4, and Serrate. Target Notch transcription factors include Hey1, Hey2, and Hes1.

The DNA and protein sequences for Notch-1 (SEQ ID NOs: 14 and 15, respectively) are published and disclosed as Genbank Accession Numbers NM_017617. Likewise, the DNA and protein sequences for various forms of Notch (including 2-4) are publicly available and included herein as SEQ ID NOs: 16-21. In addition, the DNA and protein sequences for various ligands of Notch (including Jagged1, Jagged2, Jagged2 (transcript variant 2), Delta1, Delta3, Delta4, and Jagged2 (transcript variant 1)) are publicly available and included herein as SEQ ID NOs: 22-35, respectively. DNA and protein sequences for target Notch transcription factors Hey1, Hey2, and Hes1 are also publicly available and are included herein as SEQ ID NOs: 36-41, respectively.

EXAMPLE 6

SUPPRESSION OF PROX-1 INHIBITS GROWTH IN SOFT AGAR.

Since anchorage-independent growth is one of the hallmarks of malignant transformation, experiments were conducted to assess the effects of Prox-1

suppression on the growth of SW480R cells in soft agar. SW480R cells were transfected with GFP siPRNA, Prox-1siRNA A16 or Prox-1 siRNA A25 repeatedly over an 8-day period, or left untreated, and seeded in soft agar in triplicate. The number of colonies was scored after two weeks of growth. Transfection with both Prox-1 siRNAs but not the control GFP siRNA significantly decreased the number of colonies formed after two weeks of growth in soft agar (Fig. 3A).

EXAMPLE 7

REGULATION OF PROSTAGLANDIN BIOSYNTHESIS BY PROX-1

COX-2 is a key enzyme involved in the conversion of arachidonic acid into the prostaglandin precursors PGG2 and PGH2, which are further transformed into biologically active prostaglandins by the action of corresponding synthases. Prostaglandins acts through binding to the G-protein coupled prostanoid receptors and they are rapidly inactivated by the action of 15-prostaglandin dehydrogenase (15-PGDH). COX-2 is overexpressed in the majority of colorectal cancers and in about half of colonic adenomas, suggesting that the increased PG production is important for tumor growth. In support of this view, treatment with non-steroid anti-inflammatory drugs, which acts as inhibitors of COX-2, significantly reduces the risk of developing colon cancer (Gupta, R. A. & Dubois, R. N., *Nat Rev Cancer* 1: 11-21, 2001). Accordingly, contemplated herein is a method of alleviating colorectal cancer via the administration of a Prox-1 suppressor in combination with a COX-2 inhibitor. Cox-2 inhibitors may include the following non-steroid anti-inflammatory drugs: asprin, rofecoxib, celecoxib ,amidophen, analgin, anapyrin, feloran, indomethacin, paracetoamol, piroxicam, sedalgin, diclofenac sodium, ketoprofan, Acular®, Ocufen®, and Voltarol®.

Experiments were conducted which found that suppression of Prox-1 in SW480R cells resulted in the up-regulation of the expression of 15-PGDH and downregulation of prostaglandin D2 synthase, whereas overexpression of Prox-1 in SW480F cells down-regulated 15-PGDH and up-regulated PGD2 synthase (Affymetrix results). These data suggest that Prox-1 may be important for the control of the balance of the total PG production in tumor cells, i.e., in the presence of Prox-1 decreased expression of 15-PGDH will result in higher net amounts of biologically active prostaglandins and enhanced tumor growth.

Because SW480 cells do not express COX-2, contemplated herein are experiments to assess the effects of Prox-1 on prostanoid biosynthesis in the SW480F cells stably transfected with COX-2 or in the cell line which is known to express this enzyme, such as HCA-7. To generate COX-2 expressing cells, SW480F cells are transfected with a mixture of a COX-2 expressing vector and the plasmid bearing hygromycin resistance gene, such as pCDNA3.1hygro (Invitrogen) using Lipofectamine 2000, as described in Materials and Methods, and the stable clones are selected using 200 μg/ml hygromycin B (Calbiochem) over a period of 2-3 weeks. Individual clones are isolated and the expression of COX-2 protein is tested using Western blotting. Functionality of COX-2 may be further verified in COX-2 expressing clones in comparison to the control cells, using ELISA to monitor PGE2 production according to the manufacturer's instructions (Cayman Chemical). To test the effects of Prox-1 on prostaglandin biosynthesis, COX-2 expressing cells can be infected with AdProx-1 or the control AdGFP virus, as described previously (Petrova et al., Embo J. 21: 4593-9), and the amount of biologically active PGE2, and total amount of metabolized PGE2 in cell conditioned medium, determined by ELISA (Cayman Chemicals). If overexpression of Prox-1 increases levels of the biologically active PGE2 *in vitro*, contemplated herein are studies to assess the link between Prox-1 overexpression and prostanoid biosynthesis *in vivo*. SW480R or HCA-7 stably overexpressing 15-PGDH will be produced using the protocol described above, and the tumorigenic potential of these cells in nude mice will be determined. In addition, contemplated are studies regarding the effects of the treatment with 15-PGDH inhibitor on growth of Prox-1 expressing or control xenografts in nude mice.

EXAMPLE 8

EFFECTS OF NOTCH SIGNAL TRANSDUCTION

To investigate the effects of altered Notch signaling in SW480R cells described herein are experiments that overexpress constitutively active Notch1, Notch2, Notch3, and Notch4 intracellular domains, as well as Jagged1, soluble Jagged1, and Jagged2 using recombinant adenoviruses. Replication-deficient adenoviruses for the expression of constitutively active Notch 1-4 intracellular domains, and Notch ligands Jagged1, Jagged2, Delta1, Delta3, Delta4, and Serrate are produced. SW480R cells are infected with adenoviruses. 48-72 h postinfection cells

are seeded in soft agar as described previously, and the number of colonies are scored after two weeks in culture. In parallel, total RNA is isolated and analysis of gene expression changes is conducted using Affymetrix® microarray according to the previously described procedures. If overexpression of Notch or its ligand results in the inhibition of cell growth in soft agar, further studies are conducted to investigate the effects of activation of Notch signaling on growth of tumors in nude mice.

EXAMPLE 9

EFFECTS OF PROX-1 SUPPRESSION ON SW480R IN NUDE MICE

Also contemplated herein are studies to assess the effects of Prox-1 suppression on the growth of SW480R tumors in nude mice. *Nu/nu* mice can be inoculated subcutaneously or intraperitoneally with 1-5 x 10^6 cells/mice using SW480R cells transfected with GFPsi RNA or Prox-1 siRNA, or transduced with the adenoviruses described in Example 8. Tumors are allowed to grow for 3-5 weeks, and tumor size measured twice a week. Animals are sacrificed by cervical dislocation, tumors excised, and processed for immunohistoshemical staining. The tumor histology, expression of differentiation markers, proliferation index and vascularization monitored using the antibodies against KI67 (proliferation), mucin, galectin-2, p21cip1 (differentiation), PECAM-1 and vWF (blood vessel markers), and the standard immunostaining protocols.

To assess of the effects of Prox-1-dependent genes, such as 15-PGDH, on prostaglandin metabolism and tumor growth *in vivo*, SW480R or HCA-7 cells recombinantly overexpressing 15-PGDH and control cells, are implanted subcutaneously into the *nu/nu* mice, and tumor growth and differentiation studied. In order to confirm the specificity of 15-PGDH effects, a subset of the control and 15-PGDH overexpressing tumor-bearing animals are treated with the 15-PGDH inhibitor CAY10397, administered intravenously, or in drinking water.

EXAMPLE 10

ANALYSIS OF PROX-1 IN NATURAL COLORECTAL TUMORS

Experiments to asses the expression of Prox-1 in a mouse model of human familial adenomatous polyposis, Apc min/+ are also contemplated herein. The Apc min/+ mice bear a truncating mutation in one allele of *Apc* gene, and develop

multiple intestinal polyps, which further progress to adenocarcinoma. Mice are commercially available from JAX. As another cancer model, SMAD3 deficient mice, which develop invasive colorectal cancer, is available. The DNA and protein sequences for APC (SEQ ID NOs: 42 and 43, respectively) are published and disclosed as Genbank Accession Number NM_000038.

Administration of a Prox-1 inhibitor and a placebo to mice of the above-described models is also contemplated. Prox-1 inhibitors and administration thereof are described herein. Prox-1 inhibitors available for administration include, but are not limited to, antisense oligonucleotides, siRNA constructs, or dominant negative proteins. Monitoring of the mice post-administration is contemplated to evaluate the effects of adenocarcinoma and colorectal cancer development and growth. Among the results are measurements of the speed of tumor growth in mice that received the Prox-1 inhibitor versus mice that received the placebo, thus, providing a beneficial efficacy model for the particular Prox-1 inhibitor. Also contemplated are methods for screening Prox-1 levels in family members with familial adenomatous polyposis. Methods for screening Prox-1 levels are described herein. Administration of a prophylactic to protect from progression, or the onset of cancer, is contemplated where elevated levels of Prox-1 are observed.

EXAMPLE 11

DETECTION OF PROX-1 PROTEIN EXPRESSION IN COLORECTAL CANCER

As described above, measuring Prox-1 protein expression in colon tissues may be a useful tool for diagnosing colon cancer and/or premalignancies. Prox-1 mRNA can be detected in colorectal cancer tissues as described in Example 2. The following prospective example may be conducted to determine whether Prox-1 protein correlates with Prox-1 transcript expression in colorectal cancer tissue. The immunohistochemical analysis can be carried out as follows using an anti-human Prox-1 antibody directed against the human Prox-1 peptide, as described in Example 1.

The tissues for screening are snap frozen in liquid nitrogen after dissection, embedded in OCT compound, and sectioned. Sections are fixed on –20°C methanol for 10 min, and processed for staining.

To enhance epitope recovery, the tissues may undergo steam induced epitope recovery with a retrieval solution, including several different SHIER solutions with and without enzyme digestion at two different concentrations. The tissues can then be heated in the capillary gap in the upper chamber of a Black and Decker Steamer as described in Ladner *et al.* (*Cancer Research*, 60: 3493-3503, 2000).

Automated immunohistochemistry is carried out with the TECHMATE 1000 or TECHMATE 500 (BioTek Solutions, Ventura Medical System). Specifically, the tissues are blocked with 3% and 10 % normal goat serum for 15 and 30 minutes respectively. Subsequently, the tissues are incubated with the primary antibody (anti-Prox-1 antibody) for 60 minutes at 3.0 *g/ml. The tissues are stained with the biotinylated goat-anti-rabbit IgG secondary antibody for 25 minutes. Optimal results are obtained with overnight incubation. To ensure the staining procedure is working appropriately, anti-vimentin is used as a positive control and rabbit IgG is used as a negative control.

The antibody binding is detected by an avidin-biotin based tissue staining system where horse-radish peroxidase is used as a reporter enzyme and DAB (3,3'-Diaminobenzididine Tetrahydrochloride) is used as a chromogen. Specifically, the endogenous peroxides are blocked for 30 minutes, the avidin-biotin complex reagent is added and then the tissues are incubated in DAB for a total of 15 minutes. Finally, the tissues are counterstained with hemotoxylin to assess cell and tissue morphology.

The slides are mounted in Aquamount, and the tissues are examined visually under a light microscope. Tissue that is positive for increased Prox-1 protein expression as compared to healthy colon tissue, or other cancer tissues, indicate colorectal cancer and/or premalignant lesions.

While this prospective example provide one means of detecting colon cancer, other means will be obvious to those with skill in the art. Various options for detecting Prox-1 expression, and, therefore screen for colon cancer, include, among others, ELISA-based techniques and Western blotting techniques.

EXAMPLE 12

EXPRESSION PATTERN OF PROX-1 IN NORMAL COLONIC EPITHELIUM

Studies were conducted to compare Prox-1 expression in normal cololnic epithelium. In normal colonic mucosa, all Prox-1 expressing cells were positive for the intestinal epithelial transcription factor CDX2. There was no overlap with the expression of MUC2, expressed by the goblet cells; however, a subset of Prox-1 positive cells also expressed the pan-neuroendocrine marker chromogranin A. Also observed was weaker but significant Prox-1 expression in the bottom of the crypts below the cell proliferation zone identified by staining for the Ki67 antigen.

Colonic epithelium is composed of the slowly dividing stem cells located in the bottom of the crypt, the cell proliferation zone with transient amplifying cells, which give rise to the three main colonic epithelial cell types, and terminally differentiated cells, located in the upper part of the crypts. The location of Prox-1 positive cells at the base of the crypts, therefore, corresponded to the position of the intestinal stem cells. (Bach, S. P., Renehan, A. G. & Potten, C. S., *Carcinogenesis* 21, 469-76 (2000); Potten, C. S., Kellett, M., Roberts, S. A., Rew, D. A. & Wilson, G. D., *Gut* 33, 71-8 (1992)) A similar staining pattern was observed in the murine descending colon, whereas the duodenal epithelium was negative for Prox-1. Expression of $p21^{CIP1/WAF1}$ marks the differentiated compartment of colonic crypts independently of the cell type (Doglioni, C. et al., *J Pathol* 179, 248-53 (1996)). Accordingly, studies were conducted regarding the expression of Prox-1 in relation to $p21^{CIP1/WAF1}$. All Prox-1 positive cells located at the bottom of the crypts were negative for $p21^{CIP1/WAF1}$; however, most of the rare Prox-1 positive cells present in the upper parts of the crypts were also negative for $p21^{CIP1/WAF1}$, demonstrating a mutually exclusive relation between Prox-1 expression and terminal differentiation. p21(CIP1)/(WAF1) (CDKN1) sequences are published and disclosed as Genbank Accession Numbers NM_078467 and NM_000389. These variants (1) and (2) encode the same protein.

Based on the data implicating Prospero/Prox-1 in cell fate determination in other cell types, and on its expression pattern in colonic epithelial cells it is contemplated that Prox-1 may be involved in the regulation of the

neuroendocrine cell fate as well as the stem cell phenotype. This hypothesis is supported by the fact that PROX-1 is overexpressed in intestinal neoplasms from $Apc^{min/+}$ mice and that its expression is regulated by TCF/ß-catenin pathway in vitro (see Examples 13 and 14). This hypothesis is also in agreement with previous results showing that targeted inactivation of Tcf7l2 gene encoding TCF-4 leads to the depletion of intestinal stem cell compartment and loss of neurodendocrine lineage (Korinek, V. et al., *Nat Genet* 19, 379-83 (1998)).

EXAMPLE 13

PROX-1 IS OVEREXPRESSED IN INTESTINAL NEOPLASMS FROM $APC^{min/+}$ MICE , BUT NOT FROM $Ltbp4^{-/-}$ DEFICIENT MICE

Studies were also conducted to assess Prox-1 expression in $Apc^{min/+}$ mice. A truncating germline mutation in the Apc gene together with somatic inactivation of the remaining wild type allele, lead to abnormal ß-catenin/TCF signaling in intestinal epithelial cells of $Apc^{min/+}$ mice and development of multiple intestinal polyps (Luongo, C., Moser, A. R., Gledhill, S. & Dove, W. F., *Cancer Res* 54, 5947-52 (1994); Su, L. K. et al., *Science* 256, 668-70 (1992)). High levels of Prox-1 in intestinal neoplasms of $Apc^{min/+}$ mice were observed. Prox-1 mRNA and protein were present in tumor cells with high cytoplasmic and nuclear ß-catenin levels, but not in the differentiating cells of the neighboring normal glands with membrane localization of ß-catenin.

Mutation in genes regulating TGFß signaling pathway, such as TGFRII and SMAD4 occur in human colorectal cancer, and targeted inactivation of TGF-ß1 binding protein LTBP-4 leads to colon cancer in mice (White, R. L., Cell 92, 591-2 (1998); Sterner-Kock, A. et al., Genes Dev. 16, 2264-73 (2002)). Studies were conducted to assess Prox-1 expression in Ltpb4-/- mice. In contrast to the results from Apc min/+, accumulation of Prox-1 in the colonic adenocarinomas from Ltpb4-/- mice, which generally preserve normal distribution of ß-catenin, was not observed. These results strongly suggest that Prox-1 is a target of APC/ ß-catenin/TCF pathway in vivo. Tumors from Ltpb4-/- mice had strongly increased number of lymphatic vessels, positive both for Prox-1 and LYVE-1.

EXAMPLE 14

PROX-1 EXPRESSION IS REGULATED BY ß-CATENIN/TCF PATHWAY AND DNA METHYLATION

Further studies were conducted using SW480R cell line as an in vitro model to investigate the role of Prox-1 in colorectal carcinoma. Suppression of Prox-1 expression using two different siRNAs (SEQ ID NOS: 4, 5, 6, and 7) did not affect the activity of a β-catenin/TCF-responsive reporter, the nuclear localization of β-catenin, or the cellular content of active, non-phosphorylated ß-catenin, confirming that Prox-1 is not acting upstream of this pathway. In contrast, suppression of ß-catenin using two independent siRNAs resulted in almost complete disappearance of Prox-1 mRNA and protein. In line with this finding, suppression of Prox-1 was also observed in SW480R cells transfected with dominant negative mutant of TCF4, which disrupts ß-catenin/TCF mediated transcription (Morin PJ, et al., *Science* 1997 Mar 21;275(5307):1787-90). However, overexpression of $p21^{CIP1/WAF1}$, shown to induce cell differentiation in colorectal carcinoma cells (van de Wetering, M. et al., *Cell* 111, 241-50 (2002)), did not modify Prox-1 levels. Taken together, these data show that Prox-1 lies downstream of ß-catenin/TCF4 and upstream of $p21^{CIP1/WAF1}$.

Also observed was increased expression of several known β-catenin/TCF-4 target genes, such as CD44, ENC1 and ID2 in the absence of Prox-1 (Table II, (Fujita *et al.*, 2001; Rockman *et al.*, 2001; Wielenga *et al.*, 1999)), while others such as $p21^{CIP1/WAF1}$, annexin A1, and OB-cadherin were induced upon suppression of either ß-catenin or Prox-1. These results underline the complexity of the regulatory cascade initiated by ß-catenin/TCF in CRC cells and suggest that concerted regulation by Prox-1 and other ß-catenin/TCF targets is necessary for neoplastic growth.

Studies were also conducted to compare the activation of ß-catenin/TCF signaling pathway in SW480R and SW480A cells. The SW480R cells had slightly more active ß-catenin and displayed a two-fold increase in the activation of the TCF-responsive promoter TopFLASH; however, both cell lines clearly displayed nuclear localization of ß-catenin as previously reported (Palmer, H. G. et al., *J Cell Biol* 154, 369-87 (2001)). These observations, together with the fact that abnormal ß-catenin/TCF pathway signaling is a feature of the majority of colorectal

cancer cell lines, suggest that ß-catenin/TCF activation is necessary but not sufficient for the induction of Prox-1 expression in colorectal cancer.

DNA methylation is frequently abnormal in colorectal cancer, and it was reported recently that Prox-1 expression is suppressed in human hematological cell lines due to hypermethylation of CpG islands in intron 1 of Prox-1 (Nagai, H. et al., *Genes Chromosomes Cancer* 38, 13-21 (2003)). Treatment of SW480A cells with the inhibitor of DNA methyltransferases 5-aza-2'-deoxycytidine did not result in the increase of Prox-1 mRNA, while there was increase in the expression of TIMP3. In contrast, 5-aza-2'-deoxycytidine almost completely suppressed Prox-1 expression in SW480R cells, suggesting that, at least in this cell type, the regulation of Prox-1 by DNA methylation is opposite to the one observed in leukemic cells.

Our finding that DNA demethylation decreases Prox-1 mRNA levels suggests the existence of a putative suppressor of Prox-1 transcription, whose expression becomes relieved upon treatment with 5-aza-2'-deoxycytidine. Since 5-aza-2'-deoxycytidine is used for the treatment of human cancers, our data also suggest that Prox-1 could be used as marker to identify the colorectal tumors which would respond favorably to this drug. Such screening of patients/tumors is intended as an aspect of the invention. The role of DNA methylation in the growth of intestinal neoplasms was previously demonstrated in mice heterozygous or hypomorphic for DNA methyltransferase 1, a major enzyme involved in the methylation of DNA. These mice do not develop intestinal adenomas when crossed with $Apc^{min/+}$ mice. In contrast, they develop lymphomas, demonstrating cell type specific effects of decreased DNA methylation for cancerous growth (Gaudet, F. et al., *Science* 300, 489-92 (2003), Eads, C. A. et al., *Cancer Res* 62, 1296-9 (2002)).

EXAMPLE 15

PROX-1 SUPPRESSION AND OVEREXPRESSION IN COLORECTAL CANCER

To characterize the effects of Prox-1 suppression and overexpression in colorectal cancer, stable colorectal cancer cell line clones inducibly expressing Prox-1 or Prox-1 targeting siRNAs are employed. Cells are implanted into laboratory animals, such as nu/nu mice, and tumor growth is studied in control mice and mice treated with doxycycline. As an alternative approach, Prox-1 or Prox-1 siRNA

expressing lentiviruses are employed to provide long-term expression in colorectal cancer cell lines in vitro and in vivo.

To inducibly suppress and overexpress Prox-1 or Prox-1 siRNAs, Prox-1 cDNA was subcloned in pTetOS vector (Sarao and Dumont, Transgenics Res., 1998) , where it is placed under the control of doxycycline regulated promoter. Prox-1 siRNAs were subcloned in pTer vector (van der Wetering et al., Embo Reports, 2003). Colorectal carcinoma cells stably expressing tTA activator may be transfected with Prox-1/TetOS or Prox-1 siRNS/pTer vectors. Clones may be selected in the presence of blasticidine and G480 and further tested for the expression of Prox-1 by immunostaining or Prox-1 siRNA by suppression of co-transfected Prox-1 in the presence of doxycycline. For production of Prox-1 lentiviruses, Prox-1 cDNA was subcloned into FUiresGFPW (Lois et al., Science , 2002). For production of Prox-1 siRNA lentiviruses, Prox-1 siRNAs 1 and 2 were subcloned into lentiviral vector pLL3.7 (Rubinson et al., Nat Genet., 2003).

Sequences of the DNA oligos used in the cloning of pLL3.7-Prox-1:

sense:

TGGTCATCTGCAAGCTGGATTTCAAGAGAATCCAGCTTGCAG ATGACCTTTTTC (SEQ ID NO 47).

antisense:

TCGAGAAAAAAGGTCATCTGCAAGCTGGATTCTCTTGAAATCCAGCTTGC AGTGACCA (SEQ ID NO 48).

pLL3.7 PROX1-2: sense:
TGAGCCAGTTTGATATGGATTTCAAGAGAATCCATATCAAACTGGCTCTTT TTTC (SEQ ID NO 49).

antisense:

TCGAGAAAAAAGAGCCAGTTTGATATGGATTCTCTTGAAAT CCATATCAAACTGCTCA (SEQ ID NO 50).

Inducible Prox-1 targeting short hairpin RNA ("shRNA") expression may also be achieved via CRE recombinase activated induction system whereby an

inactivating stuffer DNA sequence surrounded by modified loxP sites is removed from an shRNA expression cassette by the CRE recombinase activity, thus activating the shRNA expression. Alternatively a similar system may be used to inactivate shRNA expression upon introduciton of CRE recombinase. Tiscornia et al PNAS 2004, and Coumoul et al NAR 2004) described these systems.

shRNA or "short hairpin RNA" is a short sequence of RNA which makes a tight hairpin turn and can be used to silence gene expression. This small hairpin RNA was first used in a lentiviral vector. (Abbas-Terki T. *et al.*, *Hum. Gene Ther.* 13(18):2197-201 (2002)). shRNA generates siRNA in cells (An DS et al., *Hum. Gene Ther.* 14(12):1207-12 (2003)).

To study the effects of Prox-1 overexpression in vivo, transgenic mice overexpressing Prox-1 under the control of intestinal-specific promoter, such as villin, Cyp1A or FABPi are created using standard techniques. The proliferation and differentiation status of intestinal epithelial cells is studied by staining of intestinal tissues for PCNA, Ki67, CDKN1A, mucins, lysozyme, chromogranin A and carboxipeptidases II and IV. The crossing of Prox-1 transgenic animals with $Apc^{min/+}$ mice permits determination of whether Prox-1 overexpression influences the number and size of intestinal polyps in this mouse model of colorectal cancer.

Specifically, for *in vivo* studies of Prox-1 in intestinal differentiation, Prox-1 cDNA was subcloned in p12.4Vill plasmid, which places it under the control of 12.4 kb mous villin promoter (Madison et al., J.Biol.Chem.2002, genomic contig NT_039170). The construct may be used for the production of villin- Prox-1 transgenic mice, which will overexpress Prox-1 at the sites of villin expression, *i.e.* intestinal epithelial cells. Also contemplated is subcloning Prox-1 cDNA into the vector z/AP (Lobe et al., Dev. Biol, 1999), to be able conditionally express Prox-1 in any given tissue. In this approach Prox-1 cDNA is placed between the *loxP* sites, and it is not expressed until Cre recombinase is present in the same cell. Excision of loxP sites places the transgene under the control of chicken ß-actin promoter . To achieve intestinal specific overexpression of Prox-1 the transgenic animals containing z/AP-Prox-1 expression cassettes in their genomes may be crossed with villin-Cre mice (Madison et al., J.Biol.Chem.2002). The latter approach may be preferable to the villin-PROX1 overexpression because of potentially higher expression levels of the

transgene. Also contemplated in cloning Prox-1 cDNA under the control of rat Fabpi promoter (Rottman and Gordon, J. Biol. Chem., 1993, genomic contig NW_047627) or Cyp1A promoter (Sansom et al., Genes Dev., 2004, genomic contig NT_039474). The latter promoter has an advantage of being inducible upon administration of ß-naphtoflavone. All of these transgenic mice are contemplated as aspects of the invention.

EXAMPLE 16

DOMINANT NEGATIVE MUTANTS OF PROX-1

Further contemplated herein are dominant negative mutants of Prox-1. Specifically, a Prox-1 mutant protein lacking the transactivation domains or DNA binding domains may act in a dominant negative manner. Experiments to investigate this hypothesis may be conducted by producing a truncated form of Prox-1 lacking the last 60 amino acids or the first 575 amino acids. Disruption of the DNA binding domain entails truncation of the protein to exclude amino acids 572-634 of SEQ ID NO. 3, based on homology to Prospero (*Drosophila*). Disruption of the transactivation domain entails the deletion of amino acids 635-737. These proteins may then be tested for their ability to repress the induction of Prox-1 target genes upon co-transfection with the wt Prox-1. If such an effect is observed, the construct can be used for the generation of transgenic animals with the purpose of suppression of Prox-1 effects in vivo, or for the anti- Prox-1 therapies in colorectal cancer.

The foregoing examples are intended to be illustrative of the invention and not intended to limit the claims which define the invention. All patent, journal, and other literature cited herein is incorporated herein by reference in the entirety.

While the invention is described specifically with respect to Prox-1, there are other genes described in tables herein that are differentially expressed. All materials and methods described herein are applicable to the genes described in the tables.

Claims:

1. A method of screening colon tissue for a pathological condition, said method comprising:

measuring Prox-1 expression in a biological sample that comprises colon tissue from a mammalian subject, wherein elevated Prox-1 expression in the colon tissue correlates with a pathological phenotype.

2. A method according to claim 1, comprising comparing Prox-1 expression in the colon tissue to Prox-1 expression in healthy colon tissue, wherein increased Prox-1 expression in the colon tissue from the mammalian subject correlates with a pathological phenotype.

3.. A method according to claim 1 or 2, further comprising a step, prior to said measuring step, of obtaining the biological sample comprising colon tissue from a mammalian subject.

4. The method according to any one of claims 1-3, wherein the pathological condition is colon cancer, and wherein increased Prox-1 expression in the colon tissue is indicative of a cancerous or precancerous condition.

5. The method according to any one of claims 1-4, wherein the measuring comprises measuring Prox-1 protein in the biological sample.

6. The method of claim 5, wherein the measuring comprises contacting the colon tissue with a Prox-1 antibody or antigen-binding fragment thereof.

7. The method of any one of claims 1-6, wherein the measuring comprises measuring Prox-1 mRNA in the colon tissue.

8. The method of claim 7, wherein the measuring comprises *in situ* hybridization to measure Prox-1 mRNA in the colon sample.

9. The method of claim 7, wherein the measuring comprises steps of isolating mRNA from the colon tissue and measuring Prox-1 mRNA in the isolated mRNA.

10. The method according to any one of claims 1-9, wherein the measuring comprises quantitative polymerase chain reaction (PCR) to quantify Prox-1 mRNA in the colon tissue relative to Prox-1 mRNA in healthy colon tissue.

11. A method according to any one of claims 1-10, further comprising measuring expression of at least one gene selected from the group consisting of CD44, Enc1, and ID2 in the colon tissue, wherein elevated Prox-1 expression and elevated expression of the at least one gene in the colon tissue correlate with a pathological phenotype.

12. A method according to any one of claims 1-11, further comprising measuring activation of -catenin/TCF pathway in the colon tissue, wherein activation of the -catenin/TCF pathway and elevated Prox-1 expression in the colon tissue correlate with a pathological phenotype.

13. A method according to claim 12, wherein activation of the -catenin/TCF pathway is measured by at least one indicator in the colon tissue selected from the group consisting of: mutations in an APC gene; mutations in a -catenin gene; and nuclear localization of -catenin.

14. The method according to any one of claims 1-13, wherein the mammalian subject is a human.

15. A method according to claim 14, further comprising a step of administering to a human subject identified as having a pathological condition characterized by increased Prox-1 expression in colon tissue a composition comprising a Prox-1 inhibitor.

16. Use of a molecule that suppresses expression or activity of Prox-1 in the manufacture of a medicament for the treatment of colorectal cancer.

17. A method of inhibiting the growth of colorectal cancer cells in a mammalian subject comprising the step of:

administering to the subject a composition comprising a molecule that suppresses expression or activity of Prox-1, thereby inhibiting the growth of colon carcinoma cells.

18. A method or use according to claim 16 or 17, wherein the molecule suppresses Prox-1 expression.

19. A method or use according to any one of claims 16-18, comprising a step of identifying a mammalian subject with a colon cancer characterized by increased Prox-1 expression, wherein the composition is administered after the identifying step.

20. A method or use according to any one of claims 16-19, wherein the cancer is selected from a colorectal adenoma and a colorectal carcinoma.

21. The method or use according to any one of claims 16-20, wherein the composition further comprises a pharmaceutically acceptable diluent, adjuvant, or carrier medium.

22. The method or use according to any one of claims 16-21, wherein the molecule comprises an antisense oligonucleotide that inhibits Prox-1 expression.

23. The method or use according to any one of claims 16-21, wherein the molecule comprises micro-RNA that inhibits Prox-1 expression.

24. The method or use according to any one of claims 16-21, wherein the molecule comprises short interfering RNA (siRNA) that inhibits Prox-1 expression.

25. The method or use of claim 24, wherein the siRNA comprises at least one nucleotide sequence set forth in SEQ ID NOS: 4, 5, 6, and 7.

26. The method or use according to any one of claims 16-21, wherein the molecule comprises a zinc finger protein that inhibits Prox-1 expression.

27. The method or use according to any one of claims 16-21, wherein the molecule comprises a dominant negative form of Prox-1 protein, or an expression vector containing a nucleotide sequence encoding the dominant negative Prox-1 protein.

28. The method or use of claim 27, wherein the dominant negative form of Prox-1 protein has a disrupted DNA binding domain.

29. The method or use of claim 27, wherein the dominant negative form of Prox-1 protein has a disrupted transactivation domain.

30. The method or use according to any one of claims 16-21, wherein the molecule comprises short hairpin RNA (shRNA) that inhibits Prox-1 expression.

31. The method according to any one of claims 17-30, wherein the composition is administered in an amount effective to suppress Prox-1 expression and increase Notch 1 signaling.

32. The use according to any one of claims 16-30, wherein the molecule is present in the composition in an amount effective to suppress Prox-1 expression and increase Notch-1 signaling.

33. The method according to any one of claims 17-31, wherein the composition is administered in and amount effective to increase 15-PDGH activity or decrease prostaglandin D2 synthase activity.

34. The method according to any one of claims 17-31, further comprising administering to the subject an inhibitor of the -catenin/TCF signaling pathway.

35. The use according to any one of claims 16-30, wherein the medicament further includes an inhibitor of the -catenin/TCF signaling pathway.

36. The method or use of claim 34 or 35, wherein the inhibitor of the -catenin/TCF signaling pathway is dominant negative form of TCF-4.

37. The method or use of claim 34 or 35, wherein the inhibitor of the -catenin/TCF signaling pathway targets TCF-4, ß-catenin, or c-myc.

38. The method according to any one of claims 17-31, further comprising administering to the subject a COX-2 inhibitor.

39. The use according to any one of claims 16-30, wherein the medicament further includes a COX-2 inhibitor.

40. The method or use of claim 38 or 39, wherein the COX-2 inhibitor is a non-steroid anti-inflammatory drug.

41. The method according to any one of claims 17-31, further comprising administering to the subject a Notch signaling pathway agonist.

42. The use according to any one of claims 16-30, wherein the medicament further includes a Notch signaling pathway antagonist.

43. The method or use according to claim 41 or 42, wherein the Notch signaling pathway agonist is a Notch ligand.

44. The method or use of claim 43, wherein the Notch ligand is Jagged1, Jagged2, Delta1, Delta3, Delta4, or Serrate.

45. The method or use of claim 41 or 42, wherein the Notch signaling pathway agonists are Notch targets Hey1, Hey2, or Hes1.

46. A method of inhibiting Prox-1 function in a mammalian subject having a disease characterized by Prox-1 overexpression in cells, comprising the step of administering to said mammalian subject a composition, said composition comprising a compound effective to inhibit Prox-1 function in cells.

47. Use of an inhibitor of Prox-1 function in mammalian cells for the manufacture of a medicament for inhibiting Prox-1 function.

48. A method of screening for a Prox-1 modulator, comprising steps of:

contacting a test molecule with Prox-1 protein, or a nucleic acid comprising a nucleotide sequence that encodes Prox-1 protein, under conditions which permit the interaction of the test molecule with the Prox-1 protein or nucleic acid;

and measuring interaction between the test molecule and Prox-1 protein or nucleic acid, wherein a test molecule that binds the Prox-1 protein or nucleic acid is identified as a Prox-1 modulator.

49. The method of claim 48, wherein the test molecule comprises a protein, a carbohydrate, a lipid, or a nucleic acid.

50. The method of claim 48, wherein the test molecule comprises a member of a chemical library.

51. The method of any one of claims 48-50, comprising measuring the binding between the test molecule and the DNA binding domain of Prox-1.

52. A method of screening for modulators of binding between a DNA and Prox-1 protein comprising steps of:

a) contacting a DNA with a Prox-1 protein in the presence and in the absence of a putative modulator compound;

b) detecting binding between the DNA and the Prox-1 protein in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in binding between the DNA and the Prox-1 protein in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

53. A method of screening for modulators of binding between a DNA and Prox-1 protein comprising steps of:

a) contacting a DNA with a Prox-1 protein in the presence and in the absence of a putative modulator compound;

b) detecting binding between the DNA and the Prox-1 protein in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in differentiation in the presence of the putative modulator compound, as compared to differentiation in the absence of the putative modulator compound.

54. A method according to any one of claims 48-53, further comprising steps of:

contacting a cell from a colorectal cancer or colorectal cancer cell line with the Prox-1 modulator; and

selecting a Prox-1 modulator that inhibits growth of the cell.

55. A method according to claim 54, further comprising:

formulating a composition comprising the selected Prox-1 modulator and a pharmaceutically acceptable carrier;

administering the composition to a mammalian subject having a colorectal cancer; and

monitoring the mammalian subject for growth, metastasis, shrinkage, or disappearance of the colorectal cancer.

56. A small interfering RNA (siRNA) molecule that comprises a sense region and an antisense region, wherein said antisense region comprises sequence complementary to a nucleotide sequence encoding Prox-1 set forth as SEQ ID NO: 2, or a fragment thereof, and wherein the sense region comprises sequence complementary to the antisense region, or a fragment thereof.

57. The siRNA molecule of claim 56, wherein said siRNA molecule comprises two nucleic acid fragments, wherein one fragment comprises the sense region and the second fragment comprises the antisense region.

58. The siRNA molecule of claim 57, wherein said sense region comprises a 3'-terminal overhang relative to the antisense region.

59. The siRNA molecule of claim 57 or 58, wherein the antisense region comprises a 3'-terminal overhang relative to the sense region.

60. The siRNA molecule of claim 59, wherein said 3'-terminal overhangs each comprise 1-5 nucleotides.

61. The siRNA molecule of claim 59, wherein said antisense region 3'-terminal nucleotide overhang is complementary to RNA encoding Prox-1.

62. The siRNA molecule according to any one of claims 56-61, wherein said complementary sequences are 18-100 nucleotides in length.

63. The siRNA molecule according to any one of claims 56-61, wherein said complementary sequences are 18-30 nucleotides in length.

64. The siRNA molecule according to any one of claims 56-61, wherein said complementary sequences are 21-23 nucleotides in length.

65. The siRNA molecule according to any one of claims 56-61, wherein said antisense region comprises sequence complementary to sequence having any of SEQ ID NOs. 4 and 6.

66. The siRNA molecule according to any one of claims 56-61, wherein said antisense region comprises sequence having any of SEQ ID NOs. 5 and 7.

67. The use of an siRNA molecule according to any one of claims 56-66 in the manufacture of a medicament for the treatment of colorectal cancer.

68. The use according to claim 16, wherein the molecule comprises a compound comprising a nucleic acid 8 to 50 nucleotides in length, wherein said compound specifically hybridizes with a polynucleotide encoding Prox-1, or hybridizes to the complement of the polynucleotide, and inhibits the expression of Prox-1 when introduced into a cell that expresses Prox-1.

69. The use of claim 68, wherein the compound is an antisense oligonucleotide.

70. The use of claim 69, wherein the antisense oligonucleotide has a sequence complementary to a fragment of SEQ ID NO: 1.

71. The use of claim 70, wherein the fragment of SEQ ID NO: 1 comprises a promoter or other control region, an exon, an intron, or an exon-intron boundary.

72. The use of claim 70, wherein the fragment of SEQ ID NO: 1 comprises an exon-intron splice junction.

73. The use of claim 70, wherein the fragment of SEQ ID NO: 1 comprises a region within 50-200 bases of an exon-intron splice junction.

74. The method or use according to any one of claims 16-21, wherein the molecule comprises an inhibitor of DNA methyltransferases, thereby inhibiting Prox-1 expression.

75. The method or use according to claim 74, wherein the inhibitor of DNA methyltransferases is 5-aza-2'-deoxycytidine.

76. The method according to any one of claims 22-31, further comprising administering to the subject an inhibitor of DNA methyltransferases.

77. The use according to any one of claims 22-30, wherein the medicament further includes an inhibitor of DNA methyltransferases.

78. The method or use of claim 76 or 77, wherein the inhibitor of DNA methyltransferases is 5-aza-2'-deoxycytidine.

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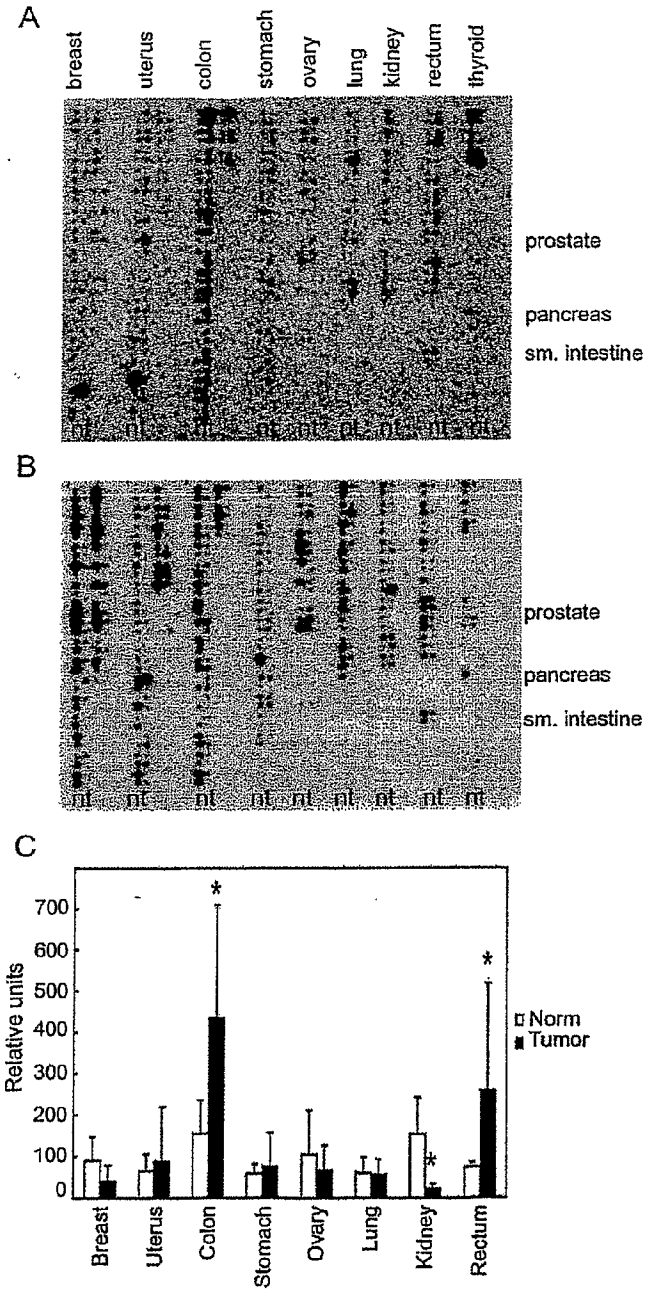

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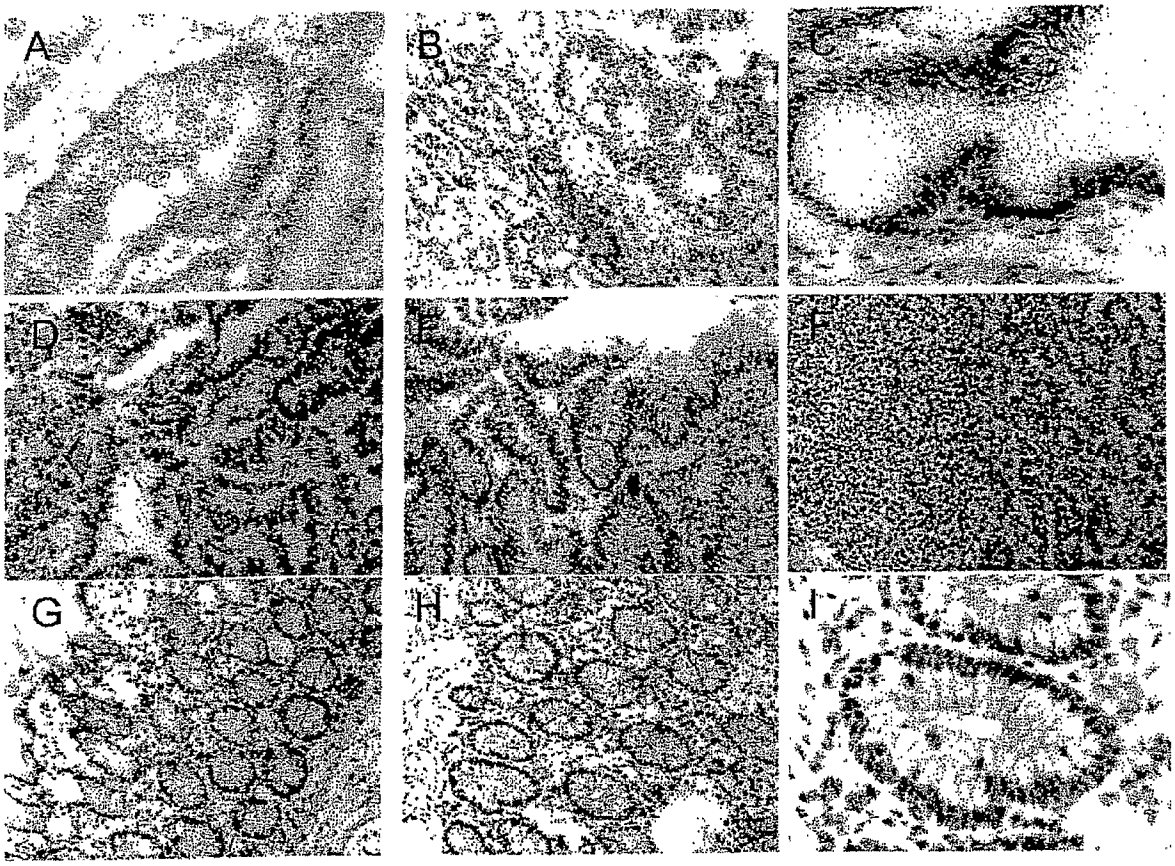

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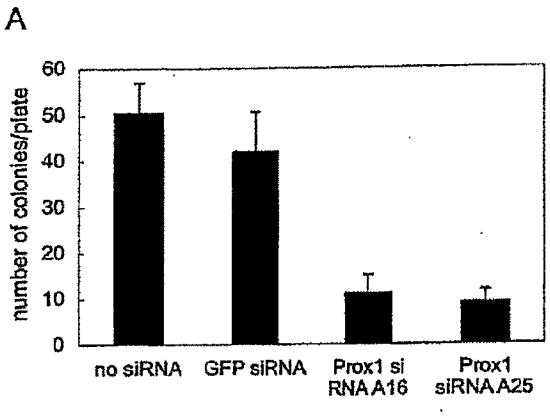
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Fig.3

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gaactcagcg ctccgctcct cccagttcct aagaggtccc gggattcttg agctgtgccc 240

agctgacgag cttttgaaga tggcacaata accgtccagt gatgcctgac catgacagca 300

cagccctctt aagccggcaa accaagagga gaagagttga cattggagtg aaaaggacgg 360

tagggacagc atctgcattt tttgctaagg caagagcaac gtttttttagt gccatgaatc 420

cccaaggttc tgagcaggat gttgagtatt cagtggtgca gcatgcagat ggggaaaagt 480

caaatgtact ccgcaagctg ctgaagaggg cgaactcgta tgaagatgcc atgatgcctt 540

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cggagcccag tttccaagcc agcggtctct ctagtacagg ctccgaagta catcaggagg 660

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acagcacaac tctacagaca gtgatgtgtc tcttgtttct actgctaaga aggtctgaaa 2940

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accccaaaag gccaaattaa aaaaaaaaaa aaaaaaa 3097

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Phe Phe Ala Lys Ala Arg Ala Thr Phe Phe Ser Ala Met Asn Pro Gln
35 40 45

Gly Ser Glu Gln Asp Val Glu Tyr Ser Val Val Gln His Ala Asp Gly
50 55 60

Glu Lys Ser Asn Val Leu Arg Lys Leu Leu Lys Arg Ala Asn Ser Tyr
65 70 75 80

Glu Asp Ala Met Met Pro Phe Pro Gly Ala Thr Ile Ile Ser Gln Leu
85 90 95

Leu Lys Asn Asn Met Asn Lys Asn Gly Gly Thr Glu Pro Ser Phe Gln
100 105 110

Ala Ser Gly Leu Ser Ser Thr Gly Ser Glu Val His Gln Glu Asp Ile
115 120 125

Cys Ser Asn Ser Ser Arg Asp Ser Pro Pro Glu Cys Leu Ser Pro Phe
130 135 140

Gly Arg Pro Thr Met Ser Gln Phe Asp Met Asp Arg Leu Cys Asp Glu

145 150 155 160

His Leu Arg Ala Lys Arg Ala Arg Val Glu Asn Ile Ile Arg Gly Met
165 170 175

Ser His Ser Pro Ser Val Ala Leu Arg Gly Asn Glu Asn Glu Arg Glu
180 185 190

Met Ala Pro Gln Ser Val Ser Pro Arg Glu Ser Tyr Arg Glu Asn Lys
195 200 205

Arg Lys Gln Lys Leu Pro Gln Gln Gln Gln Gln Ser Phe Gln Gln Leu
210 215 220

Val Ser Ala Arg Lys Glu Gln Lys Arg Glu Glu Arg Arg Gln Leu Lys
225 230 235 240

Gln Gln Leu Glu Asp Met Gln Lys Gln Leu Arg Gln Leu Gln Glu Lys
245 250 255

Phe Tyr Gln Ile Tyr Asp Ser Thr Asp Ser Glu Asn Asp Glu Asp Gly
260 265 270

Asn Leu Ser Glu Asp Ser Met Arg Ser Glu Ile Leu Asp Ala Arg Ala
275 280 285

Gln Asp Ser Val Gly Arg Ser Asp Asn Glu Met Cys Glu Leu Asp Pro
290 295 300

Gly Gln Phe Ile Asp Arg Ala Arg Ala Leu Ile Arg Glu Gln Glu Met
305 310 315 320

Ala Glu Asn Lys Pro Lys Arg Glu Gly Asn Asn Lys Glu Arg Asp His
325 330 335

Gly Pro Asn Ser Leu Gln Pro Glu Gly Lys His Leu Ala Glu Thr Leu
340 345 350

Lys Gln Glu Leu Asn Thr Ala Met Ser Gln Val Val Asp Thr Val Val
355 360 365

Lys Val Phe Ser Ala Lys Pro Ser Arg Gln Val Pro Gln Val Phe Pro
370 375 380

Pro Leu Gln Ile Pro Gln Ala Arg Phe Ala Val Asn Gly Glu Asn His
385 390 395 400

Asn Phe His Thr Ala Asn Gln Arg Leu Gln Cys Phe Gly Asp Val Ile
405 410 415

Ile Pro Asn Pro Leu Asp Thr Phe Gly Asn Val Gln Met Ala Ser Ser

420 425 430

Thr Asp Gln Thr Glu Ala Leu Pro Leu Val Val Arg Lys Asn Ser Ser
435 440 445

Asp Gln Ser Ala Ser Gly Pro Ala Ala Gly Gly His His Gln Pro Leu
450 455 460

His Gln Ser Pro Leu Ser Ala Thr Thr Gly Phe Thr Thr Ser Thr Phe
465 470 475 480

Arg His Pro Phe Pro Leu Pro Leu Met Ala Tyr Pro Phe Gln Ser Pro
485 490 495

Leu Gly Ala Pro Ser Gly Ser Phe Ser Gly Lys Asp Arg Ala Ser Pro
500 505 510

Glu Ser Leu Asp Leu Thr Arg Asp Thr Thr Ser Leu Arg Thr Lys Met
515 520 525

Ser Ser His His Leu Ser His His Pro Cys Ser Pro Ala His Pro Pro
530 535 540

Ser Thr Ala Glu Gly Leu Ser Leu Ser Leu Ile Lys Ser Glu Cys Gly
545 550 555 560

Asp Leu Gln Asp Met Ser Glu Ile Ser Pro Tyr Ser Gly Ser Ala Met
565 570 575

Gln Glu Gly Leu Ser Pro Asn His Leu Lys Lys Ala Lys Leu Met Phe
580 585 590

Phe Tyr Thr Arg Tyr Pro Ser Ser Asn Met Leu Lys Thr Tyr Phe Ser
595 600 605

Asp Val Lys Phe Asn Arg Cys Ile Thr Ser Gln Leu Ile Lys Trp Phe
610 615 620

Ser Asn Phe Arg Glu Phe Tyr Tyr Ile Gln Met Glu Lys Tyr Ala Arg
625 630 635 640

Gln Ala Ile Asn Asp Gly Val Thr Ser Thr Glu Glu Leu Ser Ile Thr
645 650 655

Arg Asp Cys Glu Leu Tyr Arg Ala Leu Asn Met His Tyr Asn Lys Ala
660 665 670

Asn Asp Phe Glu Val Pro Glu Arg Phe Leu Glu Val Ala Gln Ile Thr
675 680 685

Leu Arg Glu Phe Phe Asn Ala Ile Ile Ala Gly Lys Asp Val Asp Pro

690 695 700

Ser Trp Lys Lys Ala Ile Tyr Lys Val Ile Cys Lys Leu Asp Ser Glu
705 710 715 720

Val Pro Glu Ile Phe Lys Ser Pro Asn Cys Leu Gln Glu Leu Leu His
725 730 735

Glu

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<223> Prox-1 A16 sense

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<210> 5
<211> 21
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<223> Prox-1 A16 antisense

<400> 5
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<210> 6
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<223> Prox-1 A25 sense

<400> 6
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<210> 7
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<400> 7

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acuuguggcc guuuacgucu u 21

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cgaggacggt cggactcccg cggcgggagg agcctgttcc cctgagggta tttgaagtat 180

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tt 3362

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<212> PRT
<213> Homo sapiens

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<223> Beta-catenin

<400> 11

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20 25 30

Ser Gly Ile His Ser Gly Ala Thr Thr Thr Ala Pro Ser Leu Ser Gly
35 40 45

Lys Gly Asn Pro Glu Glu Glu Asp Val Asp Thr Ser Gln Val Leu Tyr
50 55 60

Glu Trp Glu Gln Gly Phe Ser Gln Ser Phe Thr Gln Glu Gln Val Ala
65 70 75 80

Asp Ile Asp Gly Gln Tyr Ala Met Thr Arg Ala Gln Arg Val Arg Ala
85 90 95

Ala Met Phe Pro Glu Thr Leu Asp Glu Gly Met Gln Ile Pro Ser Thr
100 105 110

Gln Phe Asp Ala Ala His Pro Thr Asn Val Gln Arg Leu Ala Glu Pro
115 120 125

Ser Gln Met Leu Lys His Ala Val Val Asn Leu Ile Asn Tyr Gln Asp
130 135 140

Asp Ala Glu Leu Ala Thr Arg Ala Ile Pro Glu Leu Thr Lys Leu Leu
145 150 155 160

Asn Asp Glu Asp Gln Val Val Val Asn Lys Ala Ala Val Met Val His
165 170 175

Gln Leu Ser Lys Lys Glu Ala Ser Arg His Ala Ile Met Arg Ser Pro
180 185 190

Gln Met Val Ser Ala Ile Val Arg Thr Met Gln Asn Thr Asn Asp Val
195 200 205

Glu Thr Ala Arg Cys Thr Ala Gly Thr Leu His Asn Leu Ser His His
210 215 220

Arg Glu Gly Leu Leu Ala Ile Phe Lys Ser Gly Gly Ile Pro Ala Leu
225 230 235 240

Val Lys Met Leu Gly Ser Pro Val Asp Ser Val Leu Phe Tyr Ala Ile
245 250 255

Thr Thr Leu His Asn Leu Leu Leu His Gln Glu Gly Ala Lys Met Ala
260 265 270

Val Arg Leu Ala Gly Gly Leu Gln Lys Met Val Ala Leu Leu Asn Lys
275 280 285

Thr Asn Val Lys Phe Leu Ala Ile Thr Thr Asp Cys Leu Gln Ile Leu
290 295 300

Ala Tyr Gly Asn Gln Glu Ser Lys Leu Ile Ile Leu Ala Ser Gly Gly
305 310 315 320

Pro Gln Ala Leu Val Asn Ile Met Arg Thr Tyr Thr Tyr Glu Lys Leu
325 330 335

Leu Trp Thr Thr Ser Arg Val Leu Lys Val Leu Ser Val Cys Ser Ser
340 345 350

Asn Lys Pro Ala Ile Val Glu Ala Gly Gly Met Gln Ala Leu Gly Leu
355 360 365

His Leu Thr Asp Pro Ser Gln Arg Leu Val Gln Asn Cys Leu Trp Thr
370 375 380

Leu Arg Asn Leu Ser Asp Ala Ala Thr Lys Gln Glu Gly Met Glu Gly
385 390 395 400

Leu Leu Gly Thr Leu Val Gln Leu Leu Gly Ser Asp Asp Ile Asn Val
405 410 415

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Val Thr Cys Ala Ala Gly Ile Leu Ser Asn Leu Thr Cys Asn Asn Tyr
            420                 425                 430

Lys Asn Lys Met Met Val Cys Gln Val Gly Gly Ile Glu Ala Leu Val
        435                 440                 445

Arg Thr Val Leu Arg Ala Gly Asp Arg Glu Asp Ile Thr Glu Pro Ala
    450                 455                 460

Ile Cys Ala Leu Arg His Leu Thr Ser Arg His Gln Glu Ala Glu Met
465                 470                 475                 480

Ala Gln Asn Ala Val Arg Leu His Tyr Gly Leu Pro Val Val Val Lys
                485                 490                 495

Leu Leu His Pro Pro Ser His Trp Pro Leu Ile Lys Ala Thr Val Gly
            500                 505                 510

Leu Ile Arg Asn Leu Ala Leu Cys Pro Ala Asn His Ala Pro Leu Arg
        515                 520                 525

Glu Gln Gly Ala Ile Pro Arg Leu Val Gln Leu Leu Val Arg Ala His
    530                 535                 540

Gln Asp Thr Gln Arg Arg Thr Ser Met Gly Gly Thr Gln Gln Gln Phe
545                 550                 555                 560

Val Glu Gly Val Arg Met Glu Glu Ile Val Glu Gly Cys Thr Gly Ala
                565                 570                 575

Leu His Ile Leu Ala Arg Asp Val His Asn Arg Ile Val Ile Arg Gly
            580                 585                 590

Leu Asn Thr Ile Pro Leu Phe Val Gln Leu Leu Tyr Ser Pro Ile Glu
        595                 600                 605

Asn Ile Gln Arg Val Ala Ala Gly Val Leu Cys Glu Leu Ala Gln Asp
    610                 615                 620

Lys Glu Ala Ala Glu Ala Ile Glu Ala Glu Gly Ala Thr Ala Pro Leu
625                 630                 635                 640

Thr Glu Leu Leu His Ser Arg Asn Glu Gly Val Ala Thr Tyr Ala Ala
                645                 650                 655

Ala Val Leu Phe Arg Met Ser Glu Asp Lys Pro Gln Asp Tyr Lys Lys
            660                 665                 670

Arg Leu Ser Val Glu Leu Thr Ser Ser Leu Phe Arg Thr Glu Pro Met
        675                 680                 685
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Ala Trp Asn Glu Thr Ala Asp Leu Gly Leu Asp Ile Gly Ala Gln Gly
690 695 700

Glu Pro Leu Gly Tyr Arg Gln Asp Asp Pro Ser Tyr Arg Ser Phe His
705 710 715 720

Ser Gly Gly Tyr Gly Gln Asp Ala Leu Gly Met Asp Pro Met Met Glu
725 730 735

His Glu Met Gly Gly His His Pro Gly Ala Asp Tyr Pro Val Asp Gly
740 745 750

Leu Pro Asp Leu Gly His Ala Gln Asp Leu Met Asp Gly Leu Pro Pro
755 760 765

Gly Asp Ser Asn Gln Leu Ala Trp Phe Asp Thr Asp Leu
770 775 780

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<213> Homo sapiens

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Gly Gly Ala Phe Val Gly Pro Arg Cys Gln Asp Pro Asn Pro Cys Leu
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Ser Thr Pro Cys Lys Asn Ala Gly Thr Cys His Val Val Asp Arg Arg
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Gly Val Ala Asp Tyr Ala Cys Ser Cys Ala Leu Gly Phe Ser Gly Pro
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Leu Cys Leu Thr Pro Leu Asp Asn Ala Cys Leu Thr Asn Pro Cys Arg
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Asn Gly Gly Thr Cys Asp Leu Leu Thr Leu Thr Glu Tyr Lys Cys Arg
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Cys Pro Pro Gly Trp Ser Gly Lys Ser Cys Gln Gln Ala Asp Pro Cys
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Ser Tyr Ile Cys His Cys Pro Pro Ser Phe His Gly Pro Thr Cys Arg
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Gln Asp Val Asn Glu Cys Gly Gln Lys Pro Gly Leu Cys Arg His Gly
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Gly Thr Cys His Asn Glu Val Gly Ser Tyr Arg Cys Val Cys Arg Ala
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Ser Pro Cys Gln Asn Gly Gly Thr Cys Arg Pro Thr Gly Asp Val Thr
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His Glu Cys Ala Cys Leu Pro Gly Phe Thr Gly Gln Asn Cys Glu Glu
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Asn Ile Asp Asp Cys Pro Gly Asn Asn Cys Lys Asn Gly Gly Ala Cys
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Val Asp Gly Val Asn Thr Tyr Asn Cys Arg Cys Pro Pro Glu Trp Thr
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Thr Ala Phe Cys Asp Cys Leu Pro Gly Phe Arg Gly Thr Phe Cys Glu
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Ser Gly Ile His Cys Glu Asn Asn Thr Pro Asp Cys Thr Glu Ser Ser
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Gly Tyr Cys Lys Cys Pro Glu Gly Phe Leu Gly Glu Tyr Cys Gln His
50 55 60

Arg Asp Pro Cys Glu Lys Asn Arg Cys Gln Asn Gly Gly Thr Cys Val
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Lys Cys Gln Thr Asp Met Asn Glu Cys Leu Ser Glu Pro Cys Lys Asn
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Cys Leu Cys Pro Pro Gly Trp Val Gly Glu Arg Cys Gln Leu Glu Asp
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Pro Cys His Ser Gly Pro Cys Ala Gly Arg Gly Val Cys Gln Ser Ser
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Val Val Ala Gly Thr Ala Arg Phe Ser Cys Arg Cys Pro Arg Gly Phe
100 105 110

Arg Gly Pro Asp Cys Ser Leu Pro Asp Pro Cys Leu Ser Ser Pro Cys
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Ala His Gly Ala Arg Cys Ser Val Gly Pro Asp Gly Arg Phe Leu Cys
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Ser Cys Pro Pro Gly Tyr Gln Gly Arg Ser Cys Arg Ser Asp Val Asp
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Pro Pro Gly Tyr Gly Gly Phe His Cys Glu Gln Asp Leu Pro Asp Cys
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Cys His Ala Gly Phe Ser Gly Pro Arg Cys Gln Thr Val Leu Ser
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Glu Pro Met Pro Thr Glu Glu Asp Glu Ala Asp Asp Thr Ser Ala
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Tyr Ala Arg Ala Asp Ala Ala Lys Arg Leu Leu Asp Ala Gly Ala
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Asp Thr Asn Ala Gln Asp His Ser Gly Arg Thr Pro Leu His Thr
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Ala Val Thr Ala Asp Ala Gln Gly Val Phe Gln Ile Leu Ile Arg
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Asn Arg Ser Thr Asp Leu Asp Ala Arg Met Ala Asp Gly Ser Thr
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Ala Leu Ile Leu Ala Ala Arg Leu Ala Val Glu Gly Met Val Glu
1910 1915 1920

Glu Leu Ile Ala Ser His Ala Asp Val Asn Ala Val Asp Glu Leu
1925 1930 1935

Gly Lys Ser Ala Leu His Trp Ala Ala Ala Val Asn Asn Val Glu
1940 1945 1950

Ala Thr Leu Ala Leu Leu Lys Asn Gly Ala Asn Lys Asp Met Gln
1955 1960 1965

Asp Ser Lys Glu Glu Thr Pro Leu Phe Leu Ala Ala Arg Glu Gly
1970 1975 1980

Ser Tyr Glu Ala Ala Lys Leu Leu Leu Asp His Phe Ala Asn Arg
1985 1990 1995

Glu Ile Thr Asp His Leu Asp Arg Leu Pro Arg Asp Val Ala Gln
2000 2005 2010

Glu Arg Leu His Gln Asp Ile Val Arg Leu Leu Asp Gln Pro Ser
2015 2020 2025

Gly Pro Arg Ser Pro Pro Gly Pro His Gly Leu Gly Pro Leu Leu
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Cys Pro Pro Gly Ala Phe Leu Pro Gly Leu Lys Ala Ala Gln Ser
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Gly Ser Lys Lys Ser Arg Arg Pro Pro Gly Lys Ala Gly Leu Gly
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Pro Gln Gly Pro Arg Gly Arg Gly Lys Lys Leu Thr Leu Ala Cys
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Ser Leu Asp Ser Pro Arg Pro Phe Gly Gly Pro Pro Ala Ser Pro
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Pro Pro Tyr Leu Ala Val Pro Gly His Gly Glu Glu Tyr Pro Val
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Cys Gln Ala Lys Leu Glu Asp Pro Cys Pro Pro Ser Phe Cys Ser Lys
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Cys Ala Pro Pro Glu Asp Asn Cys Thr Cys His His Gly His Cys Gln
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Cys Leu Asn Gly Gly Ser Cys Asn Pro Ser Pro Gly Gly Tyr Tyr Cys
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Pro Leu Ser Ser Cys Gln Lys Ala Ala Leu Ser Gln Gly Ile Asp Val
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Tyr Phe Cys His Cys Pro Pro Gly Phe Gln Gly Ser Leu Cys Gln Asp
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Lys Val Thr Pro Thr Gly Pro Cys Ser Tyr Gly His Gly Ala Thr Pro
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Val Leu Gly Gly Asn Ser Phe Tyr Leu Pro Pro Ala Gly Ala Ala Gly
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Asp Arg Ala Arg Ala Arg Ala Arg Ala Gly Gly Asp Gln Asp Pro Gly
        115                 120                 125

Leu Val Val Ile Pro Phe Gln Phe Ala Trp Pro Arg Ser Phe Thr Leu
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Ile Val Glu Ala Trp Asp Trp Asp Asn Asp Thr Thr Pro Asn Glu Glu
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Leu Leu Ile Glu Arg Val Ser His Ala Gly Met Ile Asn Pro Glu Asp
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Arg Trp Lys Ser Leu His Phe Ser Gly His Val Ala His Leu Glu Leu
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Gln Tyr Gly Asn Lys Ala Cys Met Asp Gly Trp Met Gly Lys Glu Cys
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Lys Glu Ala Val Cys Lys Gln Gly Cys Asn Leu Leu His Gly Gly Cys
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Thr Val Pro Gly Glu Cys Arg Cys Ser Tyr Gly Trp Gln Gly Arg Phe
            260                 265                 270

Cys Asp Glu Cys Val Pro Tyr Pro Gly Cys Val His Gly Ser Cys Val
        275                 280                 285

Glu Pro Trp Gln Cys Asn Cys Glu Thr Asn Trp Gly Gly Leu Leu Cys
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Asp Lys Asp Leu Asn Tyr Cys Gly Ser His His Pro Cys Thr Asn Gly
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Ser Asn Pro Cys Ala Asn Gly Gly Ser Cys His Glu Val Pro Ser Gly
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Phe Glu Cys His Cys Pro Ser Gly Trp Ser Gly Pro Thr Cys Ala Leu
    370                 375                 380

Asp Ile Asp Glu Cys Ala Ser Asn Pro Cys Ala Ala Gly Gly Thr Cys
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Val Asp Gln Val Asp Gly Phe Glu Cys Ile Cys Pro Glu Gln Trp Val
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Gly Ala Thr Cys Gln Leu Asp Ala Asn Glu Cys Glu Gly Lys Pro Cys
            420                 425                 430

Leu Asn Ala Phe Ser Cys Lys Asn Leu Ile Gly Gly Tyr Tyr Cys Asp
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Cys Ile Pro Gly Trp Lys Gly Ile Asn Cys His Ile Asn Val Asn Asp
    450                 455                 460

Cys Arg Gly Gln Cys Gln His Gly Gly Thr Cys Lys Asp Leu Val Asn
465                 470                 475                 480

Gly Tyr Gln Cys Val Cys Pro Arg Gly Phe Gly Gly Arg His Cys Glu
                485                 490                 495

Leu Glu Arg Asp Glu Cys Ala Ser Ser Pro Cys His Ser Gly Gly Leu
            500                 505                 510

Cys Glu Asp Leu Ala Asp Gly Phe His Cys His Cys Pro Gln Gly Phe
        515                 520                 525

Ser Gly Pro Leu Cys Glu Val Asp Val Asp Leu Cys Glu Pro Ser Pro
    530                 535                 540

Cys Arg Asn Gly Ala Arg Cys Tyr Asn Leu Glu Gly Asp Tyr Tyr Cys
545                 550                 555                 560

Ala Cys Pro Asp Asp Phe Gly Gly Lys Asn Cys Ser Val Pro Arg Glu
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Pro Cys Pro Gly Gly Ala Cys Arg Val Ile Asp Gly Cys Gly Ser Asp
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Leu Gly Gln Pro Cys Arg Asn Gly Gly Thr Cys Ile Asp Glu Val Asp
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Ala Phe Arg Cys Phe Cys Pro Ser Gly Trp Glu Gly Glu Leu Cys Asp
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Thr Asn Pro Asn Asp Cys Leu Pro Asp Pro Cys His Ser Arg Gly Arg
675 680 685

Cys Tyr Asp Leu Val Asn Asp Phe Tyr Cys Ala Cys Asp Asp Gly Trp
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Lys Gly Lys Thr Cys His Ser Arg Glu Phe Gln Cys Asp Ala Tyr Thr
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Cys Ser Asn Gly Gly Thr Cys Tyr Asp Ser Gly Asp Thr Phe Arg Cys
725 730 735

Ala Cys Pro Pro Gly Trp Lys Gly Ser Thr Cys Ala Val Ala Lys Asn
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785 790 795 800

Gly Gly Ile Cys Val Asp Gly Val Asn Trp Phe Arg Cys Glu Cys Ala
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Pro Gly Phe Ala Gly Pro Asp Cys Arg Ile Asn Ile Asp Glu Cys Gln
820 825 830

Ser Ser Pro Cys Ala Tyr Gly Ala Thr Cys Val Asp Glu Ile Asn Gly
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Tyr Arg Cys Ser Cys Pro Pro Gly Arg Ala Gly Pro Arg Cys Gln Glu
850 855 860

Val Ile Gly Phe Gly Arg Ser Cys Trp Ser Arg Gly Thr Pro Phe Pro
865 870 875 880

His Gly Ser Ser Trp Val Glu Asp Cys Asn Ser Cys Arg Cys Leu Asp
885 890 895

Gly Arg Arg Asp Cys Ser Lys Val Trp Cys Gly Trp Lys Pro Cys Leu
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915 920 925

Arg Cys Leu Glu Lys Ala Pro Gly Gln Cys Leu Arg Pro Pro Cys Glu
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Ser Gly Ile Arg Ser Leu Pro Ala Thr Arg Ala Val Ala Arg Asp Arg
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Val Val Leu Cys Val Trp Trp Thr Arg Lys Arg Arg Lys Glu Arg
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His Lys Asp Val Leu Tyr Gln Cys Lys Asn Phe Thr Pro Pro Pro
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Asn Gly Gly Thr Cys Ile Asp Glu Val Asp Ala Phe Arg Cys Phe Cys
610 615 620

Pro Ser Gly Trp Glu Gly Glu Leu Cys Asp Thr Asn Pro Asn Asp Cys
625 630 635 640

Leu Pro Asp Pro Cys His Ser Arg Gly Arg Cys Tyr Asp Leu Val Asn
645 650 655

Asp Phe Tyr Cys Ala Cys Asp Asp Gly Trp Lys Gly Lys Thr Cys His
660 665 670

Ser Arg Glu Phe Gln Cys Asp Ala Tyr Thr Cys Ser Asn Gly Gly Thr
675 680 685

Cys Tyr Asp Ser Gly Asp Thr Phe Arg Cys Ala Cys Pro Pro Gly Trp
690 695 700

Lys Gly Ser Thr Cys Ala Val Ala Lys Asn Ser Ser Cys Leu Pro Asn
705 710 715 720

Pro Cys Val Asn Gly Gly Thr Cys Val Gly Ser Gly Ala Ser Phe Ser
725 730 735

Cys Ile Cys Arg Asp Gly Trp Glu Gly Arg Thr Cys Thr His Asn Thr

740 745 750

Asn Asp Cys Asn Pro Leu Pro Cys Tyr Asn Gly Gly Ile Cys Val Asp
755 760 765

Gly Val Asn Trp Phe Arg Cys Glu Cys Ala Pro Gly Phe Ala Gly Pro
770 775 780

Asp Cys Arg Ile Asn Ile Asp Glu Cys Gln Ser Ser Pro Cys Ala Tyr
785 790 795 800

Gly Ala Thr Cys Val Asp Glu Ile Asn Gly Tyr Arg Cys Ser Cys Pro
805 810 815

Pro Gly Arg Ala Gly Pro Arg Cys Gln Glu Val Ile Gly Phe Gly Arg
820 825 830

Ser Cys Trp Ser Arg Gly Thr Pro Phe Pro His Gly Ser Ser Trp Val
835 840 845

Glu Asp Cys Asn Ser Cys Arg Cys Leu Asp Gly Arg Arg Asp Cys Ser
850 855 860

Lys Val Trp Cys Gly Trp Lys Pro Cys Leu Leu Ala Gly Gln Pro Glu
865 870 875 880

Ala Leu Ser Ala Gln Cys Pro Leu Gly Gln Arg Cys Leu Glu Lys Ala
885 890 895

Pro Gly Gln Cys Leu Arg Pro Pro Cys Glu Ala Trp Gly Glu Cys Gly
900 905 910

Ala Glu Glu Pro Pro Ser Thr Pro Cys Leu Pro Arg Ser Gly His Leu
915 920 925

Asp Asn Asn Cys Ala Arg Leu Thr Leu His Phe Asn Arg Asp His Val
930 935 940

Pro Gln Gly Thr Thr Val Gly Ala Ile Cys Ser Gly Ile Arg Ser Leu
945 950 955 960

Pro Ala Thr Arg Ala Val Ala Arg Asp Arg Leu Leu Val Leu Leu Cys
965 970 975

Asp Arg Ala Ser Ser Gly Ala Ser Ala Val Glu Val Ala Val Ser Phe
980 985 990

Ser Pro Ala Arg Asp Leu Pro Asp Ser Ser Leu Ile Gln Gly Ala Ala
995 1000 1005

His Ala Ile Val Ala Ala Ile Thr Gln Arg Gly Asn Ser Ser Leu

1010 1015 1020

Leu Leu Ala Val Thr Glu Val Lys Val Glu Thr Val Val Thr Gly
1025 1030 1035

Gly Ser Ser Thr Gly Leu Leu Val Pro Val Leu Cys Gly Ala Phe
1040 1045 1050

Ser Val Leu Trp Leu Ala Cys Val Val Leu Cys Val Trp Trp Thr
1055 1060 1065

Arg Lys Arg Arg Lys Glu Arg Glu Arg Ser Arg Leu Pro Arg Glu
1070 1075 1080

Glu Ser Ala Asn Asn Gln Trp Ala Pro Leu Asn Pro Ile Arg Asn
1085 1090 1095

Pro Ile Glu Arg Pro Gly Gly His Lys Asp Val Leu Tyr Gln Cys
1100 1105 1110

Lys Asn Phe Thr Pro Pro Pro Arg Arg Ala Asp Glu Ala Leu Pro
1115 1120 1125

Gly Pro Ala Gly His Ala Ala Val Arg Glu Asp Glu Glu Asp Glu
1130 1135 1140

Asp Leu Gly Arg Gly Glu Glu Asp Ser Leu Glu Ala Glu Lys Phe
1145 1150 1155

Leu Ser His Lys Phe Thr Lys Asp Pro Gly Arg Ser Pro Gly Arg
1160 1165 1170

Pro Ala His Trp Ala Ser Gly Pro Lys Val Asp Asn Arg Ala Val
1175 1180 1185

Arg Ser Ile Asn Glu Ala Arg Tyr Ala Gly Lys Glu
1190 1195 1200

<210> 28
<211> 3158
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Delta like 1 (Notch ligand)

<400> 28
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aaagaacggc gcctttggga agaggcggag accggcttta aagaaagaag tcttggtcct 180

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cgcgtggagc gaagcagcat gggcagtcgg tgcgcgctgg ccctggcggt gctctcggcc 360

ttgctgtgtc aggtctggag ctctggggtg ttcgaactga agctgcagga gttcgtcaac 420

aagaaggggc tgctggggaa ccgcaactgc tgccgcgggg gcgcggggcc accgccgtgc 480

gcctgccgga ccttcttccg cgtgtgcctc aagcactacc aggccagcgt gtcccccgag 540

ccgccctgca cctacggcag cgccgtcacc cccgtgctgg gcgtcgactc cttcagtctg 600

cccgacggcg ggggcgccga ctccgcgttc agcaacccca tccgcttccc cttcggcttc 660

acctggccgg gcaccttctc tctgattatt gaagctctcc acacagattc tcctgatgac 720

ctcgcaacag aaaacccaga aagactcatc agccgcctgg ccacccagag gcacctgacg 780

gtgggcgagg agtggtccca ggacctgcac agcagcggcc gcacggacct caagtactcc 840

taccgcttcg tgtgtgacga acactactac ggagagggct gctccgtttt ctgccgtccc 900

cgggacgatg ccttcggcca cttcacctgt ggggagcgtg gggagaaagt gtgcaaccct 960

ggctggaaag ggccctactg cacagagccg atctgcctgc ctggatgtga tgagcagcat 1020

ggattttgtg acaaaccagg ggaatgcaag tgcagagtgg gctggcaggg ccggtactgt 1080

gacgagtgta tccgctatcc aggctgtctc catggcacct gccagcagcc ctggcagtgc 1140

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cataagccct gcaagaatgg agccacctgc accaacacgg gccaggggag ctacacttgc 1260

tcttgccggc ctgggtacac aggtgccacc tgcgagctgg ggattgacga gtgtgacccc 1320

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ccacccggct tctacggcaa aatctgtgaa ttgagtgcca tgacctgtgc ggacggccct 1440

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<210> 29
<211> 723
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Delta like 1 (Notch ligand)

<400> 29

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Cys Gln Val Trp Ser Ser Gly Val Phe Glu Leu Lys Leu Gln Glu Phe
20 25 30

Val Asn Lys Lys Gly Leu Leu Gly Asn Arg Asn Cys Cys Arg Gly Gly
35 40 45

Ala Gly Pro Pro Pro Cys Ala Cys Arg Thr Phe Phe Arg Val Cys Leu
50 55 60

Lys His Tyr Gln Ala Ser Val Ser Pro Glu Pro Pro Cys Thr Tyr Gly
65 70 75 80

Ser Ala Val Thr Pro Val Leu Gly Val Asp Ser Phe Ser Leu Pro Asp
85 90 95

Gly Gly Gly Ala Asp Ser Ala Phe Ser Asn Pro Ile Arg Phe Pro Phe
100 105 110

Gly Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala Leu His
115 120 125

Thr Asp Ser Pro Asp Asp Leu Ala Thr Glu Asn Pro Glu Arg Leu Ile
130 135 140

Ser Arg Leu Ala Thr Gln Arg His Leu Thr Val Gly Glu Glu Trp Ser
145 150 155 160

Gln Asp Leu His Ser Ser Gly Arg Thr Asp Leu Lys Tyr Ser Tyr Arg
165 170 175

Phe Val Cys Asp Glu His Tyr Tyr Gly Glu Gly Cys Ser Val Phe Cys
180 185 190

Arg Pro Arg Asp Asp Ala Phe Gly His Phe Thr Cys Gly Glu Arg Gly
195 200 205

Glu Lys Val Cys Asn Pro Gly Trp Lys Gly Pro Tyr Cys Thr Glu Pro
210 215 220

Ile Cys Leu Pro Gly Cys Asp Glu Gln His Gly Phe Cys Asp Lys Pro
225 230 235 240

Gly Glu Cys Lys Cys Arg Val Gly Trp Gln Gly Arg Tyr Cys Asp Glu
245 250 255

Cys Ile Arg Tyr Pro Gly Cys Leu His Gly Thr Cys Gln Gln Pro Trp
260 265 270

Gln Cys Asn Cys Gln Glu Gly Trp Gly Gly Leu Phe Cys Asn Gln Asp
275 280 285

Leu Asn Tyr Cys Thr His His Lys Pro Cys Lys Asn Gly Ala Thr Cys
290 295 300

Thr Asn Thr Gly Gln Gly Ser Tyr Thr Cys Ser Cys Arg Pro Gly Tyr
305 310 315 320

Thr Gly Ala Thr Cys Glu Leu Gly Ile Asp Glu Cys Asp Pro Ser Pro
325 330 335

Cys Lys Asn Gly Gly Ser Cys Thr Asp Leu Glu Asn Ser Tyr Ser Cys
340 345 350

Thr Cys Pro Pro Gly Phe Tyr Gly Lys Ile Cys Glu Leu Ser Ala Met
355 360 365

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Thr Cys Ala Asp Gly Pro Cys Phe Asn Gly Gly Arg Cys Ser Asp Ser
    370                 375                 380

Pro Asp Gly Gly Tyr Ser Cys Arg Cys Pro Val Gly Tyr Ser Gly Phe
385                 390                 395                 400

Asn Cys Glu Lys Lys Ile Asp Tyr Cys Ser Ser Ser Pro Cys Ser Asn
                405                 410                 415

Gly Ala Lys Cys Val Asp Leu Gly Asp Ala Tyr Leu Cys Arg Cys Gln
            420                 425                 430

Ala Gly Phe Ser Gly Arg His Cys Asp Asp Asn Val Asp Asp Cys Ala
        435                 440                 445

Ser Ser Pro Cys Ala Asn Gly Gly Thr Cys Arg Asp Gly Val Asn Asp
    450                 455                 460

Phe Ser Cys Thr Cys Pro Pro Gly Tyr Thr Gly Arg Asn Cys Ser Ala
465                 470                 475                 480

Pro Val Ser Arg Cys Glu His Ala Pro Cys His Asn Gly Ala Thr Cys
                485                 490                 495

His Gln Arg Gly His Gly Tyr Val Cys Glu Cys Ala Arg Ser Tyr Gly
            500                 505                 510

Gly Pro Asn Cys Gln Phe Leu Leu Pro Glu Leu Pro Pro Gly Pro Ala
        515                 520                 525

Val Val Asp Leu Thr Glu Lys Leu Glu Gly Gln Gly Gly Pro Phe Pro
    530                 535                 540

Trp Val Ala Val Cys Ala Gly Val Ile Leu Val Leu Met Leu Leu Leu
545                 550                 555                 560

Gly Cys Ala Ala Val Val Val Cys Val Arg Leu Arg Leu Gln Lys His
                565                 570                 575

Arg Pro Pro Ala Asp Pro Cys Arg Gly Glu Thr Glu Thr Met Asn Asn
            580                 585                 590

Leu Ala Asn Cys Gln Arg Glu Lys Asp Ile Ser Val Ser Ile Ile Gly
        595                 600                 605

Ala Thr Gln Ile Lys Asn Thr Asn Lys Lys Ala Asp Phe His Gly Asp
    610                 615                 620

His Ser Ala Asp Lys Asn Gly Phe Lys Ala Arg Tyr Pro Ala Val Asp
625                 630                 635                 640
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Tyr Asn Leu Val Gln Asp Leu Lys Gly Asp Asp Thr Ala Val Arg Asp
645 650 655

Ala His Ser Lys Arg Asp Thr Lys Cys Gln Pro Gln Gly Ser Ser Gly
660 665 670

Glu Glu Lys Gly Thr Pro Thr Thr Leu Arg Gly Gly Glu Ala Ser Glu
675 680 685

Arg Lys Arg Pro Asp Ser Gly Cys Ser Thr Ser Lys Asp Thr Lys Tyr
690 695 700

Gln Ser Val Tyr Val Ile Ser Glu Glu Lys Asp Glu Cys Val Ile Ala
705 710 715 720

Thr Glu Val

<210> 30
<211> 1971
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Delta like 3 (Notch ligand)

<400> 30
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<210> 31
<211> 618
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Delta like 3 (Notch ligand)

<400> 31

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Ala Leu Ile Phe Leu Pro Gln Thr Arg Pro Ala Gly Val Phe Glu Leu
20 25 30

Gln Ile His Ser Phe Gly Pro Gly Pro Gly Pro Gly Ala Pro Arg Ser
35 40 45

Pro Cys Ser Ala Arg Leu Pro Cys Arg Leu Phe Phe Arg Val Cys Leu
50 55 60

Lys Pro Gly Leu Ser Glu Glu Ala Ala Glu Ser Pro Cys Ala Leu Gly
65 70 75 80

Ala Ala Leu Ser Ala Arg Gly Pro Val Tyr Thr Glu Gln Pro Gly Ala

85 90 95

Pro Ala Pro Asp Leu Pro Leu Pro Asp Gly Leu Leu Gln Val Pro Phe
100 105 110

Arg Asp Ala Trp Pro Gly Thr Phe Ser Phe Ile Ile Glu Thr Trp Arg
115 120 125

Glu Glu Leu Gly Asp Gln Ile Gly Gly Pro Ala Trp Ser Leu Leu Ala
130 135 140

Arg Val Ala Gly Arg Arg Arg Leu Ala Ala Gly Gly Pro Trp Ala Arg
145 150 155 160

Asp Ile Gln Arg Ala Gly Ala Trp Glu Leu Arg Phe Ser Tyr Arg Ala
165 170 175

Arg Cys Glu Pro Pro Ala Val Gly Thr Ala Cys Thr Arg Leu Cys Arg
180 185 190

Pro Arg Ser Ala Pro Ser Arg Cys Gly Pro Gly Leu Arg Pro Cys Ala
195 200 205

Pro Leu Glu Asp Glu Cys Glu Ala Pro Leu Val Cys Arg Ala Gly Cys
210 215 220

Ser Pro Glu His Gly Phe Cys Glu Gln Pro Gly Glu Cys Arg Cys Leu
225 230 235 240

Glu Gly Trp Thr Gly Pro Leu Cys Thr Val Pro Val Ser Thr Ser Ser
245 250 255

Cys Leu Ser Pro Arg Gly Pro Ser Ser Ala Thr Thr Gly Cys Leu Val
260 265 270

Pro Gly Pro Gly Pro Cys Asp Gly Asn Pro Cys Ala Asn Gly Gly Ser
275 280 285

Cys Ser Glu Thr Pro Arg Ser Phe Glu Cys Thr Cys Pro Arg Gly Phe
290 295 300

Tyr Gly Leu Arg Cys Glu Val Ser Gly Val Thr Cys Ala Asp Gly Pro
305 310 315 320

Cys Phe Asn Gly Gly Leu Cys Val Gly Gly Ala Asp Pro Asp Ser Ala
325 330 335

Tyr Ile Cys His Cys Pro Pro Gly Phe Gln Gly Ser Asn Cys Glu Lys
340 345 350

Arg Val Asp Arg Cys Ser Leu Gln Pro Cys Arg Asn Gly Gly Leu Cys

355 360 365

Leu Asp Leu Gly His Ala Leu Arg Cys Arg Cys Arg Ala Gly Phe Ala
370 375 380

Gly Pro Arg Cys Glu His Asp Leu Asp Asp Cys Ala Gly Arg Ala Cys
385 390 395 400

Ala Asn Gly Gly Thr Cys Val Glu Gly Gly Gly Ala His Arg Cys Ser
405 410 415

Cys Ala Leu Gly Phe Gly Gly Arg Asp Cys Arg Glu Arg Ala Asp Pro
420 425 430

Cys Ala Ala Arg Pro Cys Ala His Gly Gly Arg Cys Tyr Ala His Phe
435 440 445

Ser Gly Leu Val Cys Ala Cys Ala Pro Gly Tyr Met Gly Ala Arg Cys
450 455 460

Glu Phe Pro Val His Pro Asp Gly Ala Ser Ala Leu Pro Ala Ala Pro
465 470 475 480

Pro Gly Leu Arg Pro Gly Asp Pro Gln Arg Tyr Leu Leu Pro Pro Ala
485 490 495

Leu Gly Leu Leu Val Ala Ala Gly Val Ala Gly Ala Ala Leu Leu Leu
500 505 510

Val His Val Arg Arg Arg Gly His Ser Gln Asp Ala Gly Ser Arg Leu
515 520 525

Leu Ala Gly Thr Pro Glu Pro Ser Val His Ala Leu Pro Asp Ala Leu
530 535 540

Asn Asn Leu Arg Thr Gln Glu Gly Ser Gly Asp Gly Pro Ser Ser Ser
545 550 555 560

Val Asp Trp Asn Arg Pro Glu Asp Val Asp Pro Gln Gly Ile Tyr Val
565 570 575

Ile Ser Ala Pro Ser Ile Tyr Ala Arg Glu Val Ala Thr Pro Leu Phe
580 585 590

Pro Pro Leu His Thr Gly Arg Ala Gly Gln Arg Gln His Leu Leu Phe
595 600 605

Pro Tyr Pro Ser Ser Ile Leu Ser Val Lys
610 615

<210> 32

<211> 3383
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Delta like 4 (Notch ligand)

<400> 32
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ggtcgccgcc cagccgtagt cacctggatt acctacagcg gcagctgcag cggagccagc 180

gagaaggcca aaggggagca gcgtcccgag aggagcgcct cttttcaggg accccgccgg 240

ctggcggacg cgcgggaaag cggcgtcgcg aacagagcca gattgagggc ccgcgggtgg 300

agagagcgac gcccgagggg atggcggcag cgtcccggag cgcctctggc tgggcgctac 360

tgctgctggt ggcactttgg cagcagcgcg cggccggctc cggcgtcttc cagctgcagc 420

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tgccaccaga tgcactcatc agcaagatcg ccatccaggg ctccctagct gtgggtcaga 780

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caggctacac tggtgtggac tgtgagctgg agctcagcga gtgtgacagc aacccctgtc 1320

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Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly Val Leu Ala Ser Gly Arg
        35                  40                  45

Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg Val Cys Leu Lys His
    50                  55                  60

Phe Gln Ala Val Val Ser Pro Gly Pro Cys Thr Phe Gly Thr Val Ser
65                  70                  75                  80

Thr Pro Val Leu Gly Thr Asn Ser Phe Ala Val Arg Asp Asp Ser Ser
                85                  90                  95

Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro Phe Asn Phe Thr Trp Pro
            100                 105                 110

Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp His Ala Pro Gly Asp Asp
        115                 120                 125

Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala Leu Ile Ser Lys Ile Ala
    130                 135                 140

Ile Gln Gly Ser Leu Ala Val Gly Gln Asn Trp Leu Leu Asp Glu Gln
145                 150                 155                 160

Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser Tyr Arg Val Ile Cys Ser
                165                 170                 175

Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg Leu Cys Lys Lys Arg Asn
            180                 185                 190

Asp His Phe Gly His Tyr Val Cys Gln Pro Asp Gly Asn Leu Ser Cys
        195                 200                 205

Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln Gln Pro Ile Cys Leu Ser
    210                 215                 220

Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys Pro Ala Glu Cys Leu
225                 230                 235                 240

Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys Asn Glu Cys Ile Pro His
                245                 250                 255

Asn Gly Cys Arg His Gly Thr Cys Ser Thr Pro Trp Gln Cys Thr Cys
            260                 265                 270
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Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln Asp Leu Asn Tyr Cys
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Thr His His Ser Pro Cys Lys Asn Gly Ala Thr Cys Ser Asn Ser Gly
290 295 300

Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro Gly Tyr Thr Gly Val Asp
305 310 315 320

Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser Asn Pro Cys Arg Asn Gly
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Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr His Cys Leu Cys Pro Pro
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Gly Tyr Tyr Gly Leu His Cys Glu His Ser Thr Leu Ser Cys Ala Asp
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Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu Arg Asn Gln Gly Ala
370 375 380

Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr Gly Ser Asn Cys Glu
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Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys Ala Asn Gly Gly Gln
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Cys Leu Asn Arg Gly Pro Ser Arg Met Cys Arg Cys Arg Pro Gly Phe
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Thr Gly Thr Tyr Cys Glu Leu His Val Ser Asp Cys Ala Arg Asn Pro
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Cys Ala His Gly Gly Thr Cys His Asp Leu Glu Asn Gly Leu Met Cys
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Asp Asn Leu Ile Pro Ala Ala Gln Leu Lys Asn Thr Asn Gln Lys Lys
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Glu Leu Glu Val Asp Cys Gly Leu Asp Lys Ser Asn Cys Gly Lys Gln
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Gln Asn His Thr Leu Asp Tyr Asn Leu Ala Pro Gly Pro Leu Gly Arg
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Gly Thr Met Pro Gly Lys Phe Pro His Ser Asp Lys Ser Leu Gly Glu
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Lys Ala Pro Leu Arg Leu His Ser Glu Lys Pro Glu Cys Arg Ile Ser
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<223> Jagged2, transcript variant 1

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Cys Cys Asp Gly Asp Gly Arg Thr Thr Arg Ala Gly Gly Cys Gly His
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Asp Glu Cys Asp Thr Tyr Val Arg Val Cys Leu Lys Glu Tyr Gln Ala
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Lys Val Thr Pro Thr Gly Pro Cys Ser Tyr Gly His Gly Ala Thr Pro
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Val Leu Gly Gly Asn Ser Phe Tyr Leu Pro Pro Ala Gly Ala Ala Gly
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Asp Arg Ala Arg Ala Arg Ala Arg Ala Gly Gly Asp Gln Asp Pro Gly
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Leu Val Val Ile Pro Phe Gln Phe Ala Trp Pro Arg Ser Phe Thr Leu
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Ile Val Glu Ala Trp Asp Trp Asp Asn Asp Thr Thr Pro Asn Glu Glu
145 150 155 160

Leu Leu Ile Glu Arg Val Ser His Ala Gly Met Ile Asn Pro Glu Asp

165 170 175

Arg Trp Lys Ser Leu His Phe Ser Gly His Val Ala His Leu Glu Leu
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Gln Ile Arg Val Arg Cys Asp Glu Asn Tyr Tyr Ser Ala Thr Cys Asn
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Lys Phe Cys Arg Pro Arg Asn Asp Phe Phe Gly His Tyr Thr Cys Asp
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Gln Tyr Gly Asn Lys Ala Cys Met Asp Gly Trp Met Gly Lys Glu Cys
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Lys Glu Ala Val Cys Lys Gln Gly Cys Asn Leu Leu His Gly Gly Cys
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Thr Val Pro Gly Glu Cys Arg Cys Ser Tyr Gly Trp Gln Gly Arg Phe
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Cys Asp Glu Cys Val Pro Tyr Pro Gly Cys Val His Gly Ser Cys Val
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Glu Pro Trp Gln Cys Asn Cys Glu Thr Asn Trp Gly Gly Leu Leu Cys
290 295 300

Asp Lys Asp Leu Asn Tyr Cys Gly Ser His His Pro Cys Thr Asn Gly
305 310 315 320

Gly Thr Cys Ile Asn Ala Glu Pro Asp Gln Tyr Arg Cys Thr Cys Pro
325 330 335

Asp Gly Tyr Ser Gly Arg Asn Cys Glu Lys Ala Glu His Ala Cys Thr
340 345 350

Ser Asn Pro Cys Ala Asn Gly Gly Ser Cys His Glu Val Pro Ser Gly
355 360 365

Phe Glu Cys His Cys Pro Ser Gly Trp Ser Gly Pro Thr Cys Ala Leu
370 375 380

Asp Ile Asp Glu Cys Ala Ser Asn Pro Cys Ala Ala Gly Gly Thr Cys
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Val Asp Gln Val Asp Gly Phe Glu Cys Ile Cys Pro Glu Gln Trp Val
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Gly Ala Thr Cys Gln Leu Asp Ala Asn Glu Cys Glu Gly Lys Pro Cys
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Leu Asn Ala Phe Ser Cys Lys Asn Leu Ile Gly Gly Tyr Tyr Cys Asp

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Cys Ile Pro Gly Trp Lys Gly Ile Asn Cys His Ile Asn Val Asn Asp
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Cys Arg Gly Gln Cys Gln His Gly Gly Thr Cys Lys Asp Leu Val Asn
465 470 475 480

Gly Tyr Gln Cys Val Cys Pro Arg Gly Phe Gly Gly Arg His Cys Glu
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Leu Glu Arg Asp Glu Cys Ala Ser Ser Pro Cys His Ser Gly Gly Leu
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Cys Glu Asp Leu Ala Asp Gly Phe His Cys His Cys Pro Gln Gly Phe
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Ser Gly Pro Leu Cys Glu Val Asp Val Asp Leu Cys Glu Pro Ser Pro
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Ala Cys Pro Asp Asp Phe Gly Gly Lys Asn Cys Ser Val Pro Arg Glu
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Pro Cys Pro Gly Gly Ala Cys Arg Val Ile Asp Gly Cys Gly Ser Asp
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Ala Gly Pro Gly Met Pro Gly Thr Ala Ala Ser Gly Val Cys Gly Pro
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His Gly Arg Cys Val Ser Gln Pro Gly Gly Asn Phe Ser Cys Ile Cys
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Asp Ser Gly Phe Thr Gly Thr Tyr Cys His Glu Asn Ile Asp Asp Cys
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Ala Phe Arg Cys Phe Cys Pro Ser Gly Trp Glu Gly Glu Leu Cys Asp
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Thr Asn Pro Asn Asp Cys Leu Pro Asp Pro Cys His Ser Arg Gly Arg
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Lys Gly Lys Thr Cys His Ser Arg Glu Phe Gln Cys Asp Ala Tyr Thr

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Cys Ser Asn Gly Gly Thr Cys Tyr Asp Ser Gly Asp Thr Phe Arg Cys
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755 760 765

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785 790 795 800

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820 825 830

Ser Ser Pro Cys Ala Tyr Gly Ala Thr Cys Val Asp Glu Ile Asn Gly
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Tyr Arg Cys Ser Cys Pro Pro Gly Arg Ala Gly Pro Arg Cys Gln Glu
850 855 860

Val Ile Gly Phe Gly Arg Ser Cys Trp Ser Arg Gly Thr Pro Phe Pro
865 870 875 880

His Gly Ser Ser Trp Val Glu Asp Cys Asn Ser Cys Arg Cys Leu Asp
885 890 895

Gly Arg Arg Asp Cys Ser Lys Val Trp Cys Gly Trp Lys Pro Cys Leu
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Arg Cys Leu Glu Lys Ala Pro Gly Gln Cys Leu Arg Pro Pro Cys Glu
930 935 940

Ala Trp Gly Glu Cys Gly Ala Glu Glu Pro Pro Ser Thr Pro Cys Leu
945 950 955 960

Pro Arg Ser Gly His Leu Asp Asn Asn Cys Ala Arg Leu Thr Leu His
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Ser Gly Ile Arg Ser Leu Pro Ala Thr Arg Ala Val Ala Arg Asp Arg
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His Lys Asp Val Leu Tyr Gln Cys Lys Asn Phe Thr Pro Pro Pro
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Asp Pro Gly Arg Ser Pro Gly Arg Pro Ala His Trp Ala Ser Gly
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<210> 37
<211> 304
<212> PRT
<213> Homo sapiens

<220>
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<223> Hey-1

<400> 37

Met Lys Arg Ala His Pro Glu Tyr Ser Ser Ser Asp Ser Glu Leu Asp
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Glu Thr Ile Glu Val Glu Lys Glu Ser Ala Asp Glu Asn Gly Asn Leu
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Ser Ser Ala Leu Gly Ser Met Ser Pro Thr Thr Ser Ser Gln Ile Leu
35 40 45

Ala Arg Lys Arg Arg Arg Gly Ile Ile Glu Lys Arg Arg Arg Asp Arg
50 55 60

Ile Asn Asn Ser Leu Ser Glu Leu Arg Arg Leu Val Pro Ser Ala Phe
65 70 75 80

Glu Lys Gln Gly Ser Ala Lys Leu Glu Lys Ala Glu Ile Leu Gln Met
85 90 95

Thr Val Asp His Leu Lys Met Leu His Thr Ala Gly Gly Lys Gly Tyr
100 105 110

Phe Asp Ala His Ala Leu Ala Met Asp Tyr Arg Ser Leu Gly Phe Arg
115 120 125

Glu Cys Leu Ala Glu Val Ala Arg Tyr Leu Ser Ile Ile Glu Gly Leu

130 135 140

Asp Ala Ser Asp Pro Leu Arg Val Arg Leu Val Ser His Leu Asn Asn
145 150 155 160

Tyr Ala Ser Gln Arg Glu Ala Ala Ser Gly Ala His Ala Gly Leu Gly
165 170 175

His Ile Pro Trp Gly Thr Val Phe Gly His His Pro His Ile Ala His
180 185 190

Pro Leu Leu Leu Pro Gln Asn Gly His Gly Asn Ala Gly Thr Thr Ala
195 200 205

Ser Pro Thr Glu Pro His His Gln Gly Arg Leu Gly Ser Ala His Pro
210 215 220

Glu Ala Pro Ala Leu Arg Ala Pro Pro Ser Gly Ser Phe Gly Pro Val
225 230 235 240

Leu Pro Val Val Thr Ser Ala Ser Lys Leu Ser Leu Pro Leu Leu Ser
245 250 255

Ser Val Ala Ser Leu Ser Ala Phe Pro Phe Ser Phe Gly Ser Phe His
260 265 270

Leu Leu Ser Pro Asn Ala Leu Ser Pro Ser Ala Pro Thr Gln Ala Ala
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Asn Leu Gly Lys Pro Tyr Arg Pro Trp Gly Thr Glu Ile Gly Ala Phe
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<213> Homo sapiens

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<223> Hey-2

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ctcagattat ggcaagaaag aaaaggagag ggattataga gaaaaggcgt cgggatcgga 240

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<210> 39
<211> 337
<212> PRT
<213> Homo sapiens

<220>
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<223> Hey-2

<400> 39

Met Lys Arg Pro Cys Glu Glu Thr Thr Ser Glu Ser Asp Met Asp Glu
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Thr Ile Asp Val Gly Ser Glu Asn Asn Tyr Ser Gly Gln Ser Thr Ser
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Ser Val Ile Arg Leu Asn Ser Pro Thr Thr Thr Ser Gln Ile Met Ala
35 40 45

Arg Lys Lys Arg Arg Gly Ile Ile Glu Lys Arg Arg Arg Asp Arg Ile
50 55 60

Asn Asn Ser Leu Ser Glu Leu Arg Arg Leu Val Pro Thr Ala Phe Glu
65 70 75 80

Lys Gln Gly Ser Ala Lys Leu Glu Lys Ala Glu Ile Leu Gln Met Thr
85 90 95

Val Asp His Leu Lys Met Leu Gln Ala Thr Gly Gly Lys Gly Tyr Phe
100 105 110

Asp Ala His Ala Leu Ala Met Asp Phe Met Ser Ile Gly Phe Arg Glu
115 120 125

Cys Leu Thr Glu Val Ala Arg Tyr Leu Ser Ser Val Glu Gly Leu Asp
130 135 140

Ser Ser Asp Pro Leu Arg Val Arg Leu Val Ser His Leu Ser Thr Cys
145 150 155 160

Ala Thr Gln Arg Glu Ala Ala Ala Met Thr Ser Ser Met Ala His His
165 170 175

His His Pro Leu His Pro His His Trp Ala Ala Ala Phe His His Leu
180 185 190

Pro Ala Ala Leu Leu Gln Pro Asn Gly Leu His Ala Ser Glu Ser Thr
195 200 205

Pro Cys Arg Leu Ser Thr Thr Ser Glu Val Pro Pro Ala His Gly Ser
210 215 220

Ala Leu Leu Thr Ala Thr Phe Ala His Ala Asp Ser Ala Leu Arg Met
225 230 235 240

Pro Ser Thr Gly Ser Val Ala Pro Cys Val Pro Pro Leu Ser Thr Ser
245 250 255

Leu Leu Ser Leu Ser Ala Thr Val His Ala Ala Ala Ala Ala Ala Thr
260 265 270

Ala Ala Ala His Ser Phe Pro Leu Ser Phe Ala Gly Ala Phe Pro Met
275 280 285

Leu Pro Pro Asn Ala Ala Ala Ala Val Ala Ala Ala Thr Ala Ile Ser
290 295 300

Pro Pro Leu Ser Val Ser Ala Thr Ser Ser Pro Gln Gln Thr Ser Ser
305 310 315 320

Gly Thr Asn Asn Lys Pro Tyr Arg Pro Trp Gly Thr Glu Val Gly Ala
325 330 335

Phe

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<211> 1471
<212> DNA
<213> Homo sapiens

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<223> Hes-1

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cttgctcagt agttttgtga aagtctcaag taaaagagac acaaacaaaa aattcttttt 180

cgtgaagaac tccaaaaata aaattctcta gagataaaaa aaaaaaaaaa aggaaaatgc 240

cagctgatat aatggagaaa aattcctcgt ccccggtggc tgctacccca gccagtgtca 300

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tggagaaaag acgaagagca agaataaatg aaagtctgag ccagctgaaa acactgattt 420

tggatgctct gaagaaagat agctcgcggc attccaagct ggagaaggcg gacattctgg 480

aaatgacagt gaagcacctc cggaacctgc agcgggcgca gatgacggct gcgctgagca 540

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ccttgcaggc gccgccaccg cccccaccgg gacccggcgg cccccagcac gcgccgttcg 780

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<212> PRT
<213> Homo sapiens

<220>
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<223> Hes-1

<400> 41

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Thr Pro Ala Ser Val Asn Thr Thr Pro Asp Lys Pro Lys Thr Ala Ser
20 25 30

Glu His Arg Lys Ser Ser Lys Pro Ile Met Glu Lys Arg Arg Arg Ala
35 40 45

Arg Ile Asn Glu Ser Leu Ser Gln Leu Lys Thr Leu Ile Leu Asp Ala
50 55 60

Leu Lys Lys Asp Ser Ser Arg His Ser Lys Leu Glu Lys Ala Asp Ile
65 70 75 80

Leu Glu Met Thr Val Lys His Leu Arg Asn Leu Gln Arg Ala Gln Met
85 90 95

Thr Ala Ala Leu Ser Thr Asp Pro Ser Val Leu Gly Lys Tyr Arg Ala

100 105 110

Gly Phe Ser Glu Cys Met Asn Glu Val Thr Arg Phe Leu Ser Thr Cys
115 120 125

Glu Gly Val Asn Thr Glu Val Arg Thr Arg Leu Leu Gly His Leu Ala
130 135 140

Asn Cys Met Thr Gln Ile Asn Ala Met Thr Tyr Pro Gly Gln Pro His
145 150 155 160

Pro Ala Leu Gln Ala Pro Pro Pro Pro Pro Pro Gly Pro Gly Gly Pro
165 170 175

Gln His Ala Pro Phe Ala Pro Pro Pro Leu Val Pro Ile Pro Gly
180 185 190

Gly Ala Ala Pro Pro Pro Gly Gly Ala Pro Cys Lys Leu Gly Ser Gln
195 200 205

Ala Gly Glu Ala Ala Lys Val Phe Gly Gly Phe Gln Val Val Pro Ala
210 215 220

Pro Asp Gly Gln Phe Ala Phe Leu Ile Pro Asn Gly Ala Phe Ala His
225 230 235 240

Ser Gly Pro Val Ile Pro Val Tyr Thr Ser Asn Ser Gly Thr Ser Val
245 250 255

Gly Pro Asn Ala Val Ser Pro Ser Ser Gly Pro Ser Leu Thr Ala Asp
260 265 270

Ser Met Trp Arg Pro Trp Arg Asn
275 280

<210> 42
<211> 10386
<212> DNA
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Gln Ile Asp Leu Leu Glu Arg Leu Lys Glu Leu Asn Leu Asp Ser Ser
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Asn Phe Pro Gly Val Lys Leu Arg Ser Lys Met Ser Leu Arg Ser Tyr
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Tyr Lys Asp Ala Asn Ile Met Ser Pro Gly Ser Ser Leu Pro Ser Leu
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His Cys Val Thr Asp Glu Arg Asn Ala Leu Arg Arg Ser Ser Ala Ala
        915                 920                 925

His Thr His Ser Asn Thr Tyr Asn Phe Thr Lys Ser Glu Asn Ser Asn
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Arg Thr Cys Ser Met Pro Tyr Ala Lys Leu Glu Tyr Lys Arg Ser Ser
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Ser Leu Arg Gly Asp Asn Asp Gly Gly Gly Gly Ser Phe Ser Thr Ala
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Gln Ser Phe Ile Cys Asp Pro Asp Asp Glu Thr Phe Ile Lys Asn Ile
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Val Ser Glu Lys Leu Ala Ser Tyr Gln Ala Ala Arg Lys Asp Ser Gly
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Val Val Phe Pro Tyr Pro Leu Asn Asp Ser Ser Ser Pro Lys Ser Cys
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His Glu Glu Thr Pro Pro Thr Thr Ser Ser Asp Ser Glu Glu Glu Gln
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Lys Pro Pro His Ser Pro Leu Val Leu Lys Arg Cys His Val Ser Thr
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His Gln His Asn Tyr Ala Ala Pro Pro Ser Thr Arg Lys Asp Tyr Pro
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/008819

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/027285 A (BIONOMICS LTD. (AU)) 3 April 2003 (2003-04-03) page 3, lines 22-37; table 2 page 14, line 1 - page 15, line 11; claims 2,34-36,41,44,55,77; sequence 102	46-51, 54-56
X	US 2003/087807 A1 (GREENSPAN R.J.) 8 May 2003 (2003-05-08) claims 15,17,51	49-51, 54,55

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 2004	29/12/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Barz, W

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/008819

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PETROVA T.V. ET AL.: "Lymphatic endothelial reprogramming of vascular endothelial cells by the Prox-1 homeobox transcription factor" EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, vol. 21, no. 17, September 2002 (2002-09), pages 4593-4599, XP002309905 ISSN: 0261-4189 abstract	1-78
A	HONG Y.-K. ET AL.: "Prox1 is a master control gene in the program specifying lymphatic endothelial cell fate." DEVELOPMENTAL DYNAMICS, vol. 225, no. 3, November 2002 (2002-11), pages 351-357, XP009040935 ISSN: 1058-8388 abstract	1-78
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A	WIGLE J.T. ET AL.: "Prox1 function is required for the development of the murine lymphatic system" CELL, vol. 98, no. 6, 17 September 1999 (1999-09-17), pages 769-778, XP002309908 ISSN: 0092-8674 the whole document	1-78
A	PETROVA T.V. ET AL.: "Effects of lymphatic transcription factor Prox-1 on cell cycle progression" JOURNAL OF SUBMICROSCOPIC CYTOLOGY AND PATHOLOGY, vol. 32, no. 3, July 2000 (2000-07), page 406, XP009040762 & XITH INTERNATIONAL VASCULAR BIOLOGY MEETING; GENEVA, SWITZERLAND; SEPTEMBER 05-09, 2000 ISSN: 1122-9497 abstract	1-78

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/008819

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	XIA H. ET AL.: "siRNA-mediated gene silencing in vitro and in vivo" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, vol. 20, no. 10, October 2002 (2002-10), pages 1006-1010, XP002251054 ISSN: 1087-0156 abstract	56-67
A	BRUMMELKAMP T.R. ET AL.: "A system for stable expression of short interfering RNAs in mammalian cells" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 296, no. 5567, 2002, pages 550-553, XP002225638 ISSN: 0036-8075 abstract; figures 1,2	56-67
P,A	LOHELA M. ET AL.: "Lymphangiogenic growth factors, receptors and therapies." THROMBOSIS AND HAEMOSTASIS, vol. 90, no. 2, August 2003 (2003-08), pages 167-184, XP009040757 ISSN: 0340-6245 abstract page 168, paragraph bridging both columns; page 169, last paragraph of left column.	1-78

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/008819

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2461372 A1	03-04-2003
		EP 1430126 A1	23-06-2004
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		CA 2392963 A1	07-06-2001
		EP 1255993 A2	13-11-2002
		WO 0140519 A2	07-06-2001